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PHYSIOLOGICAL REACTIONS OF THE THYROID STIMULATING HORMONE OF THE PITUITARY. II. THE EFFECT OF NORMAL AND PATHOLOGICAL HUMAN THYROID TISSUES ON THE ACTIVITY OF THE THYROID STIMULATING HORMONE*

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INTRODUCTION

MANY investigators [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13] have demonstrated an impressive similarity between changes induced in laboratory animals treated with the thyroid stimulating hormone of the pituitary (TSH), and the clinical entity, Graves' disease. Such changes include hyperplasia of the thyroid, tachycardia, weight loss, increase in oxygen consumption, and exophthalmos. On the basis of such observations one might be tempted to conclude that the pituitary is a factor in the etiology of clinical thyrotoxicosis. However, one serious objection to such a conclusion is the fact that several investigators [14, 15, 16, 17, 18] have failed to demonstrate the thyrotropic hormone in the urine of thyrotoxic patients. Hertz and Oastler [14] found a thyroid stimulating substance in the urine of nine myxedematous patients, but were unable to demonstrate any thyrotropic effect in the urine of normal or thyrotoxic individuals. Rawson and Starr [16] found demonstrable amounts of thyrotropic substances in the urine of normal medical students. They found a strongly positive thyroid stimulating effect in the urine of three men who had had total thyroidectomies, and in the urine of a majority of non-myxedematous patients whose basal metabolic rates varied between –34 and –17. How-

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ever, there was no evidence of a thyroid stimulating substance in the urine of 12 out of 14 thyrotoxic patients studied by these investigators.

In the light of the above observations it has been suggested [19, 20, 21] that there exists a balance between the thyroid and the pituitary, and that any deficiency in the thyroid stimulates the pituitary to produce more of the thyroid stimulating hormone, and conversely, supplying the thyroid hormone reduces the anterior pituitary secretion of TSH. Salter [22] has called this the pituitary thyroid axis. On the basis of this theory one might explain the absence of any demonstrable TSH in the urine of thyrotoxic patients as being due to a suppression of the pituitary by an increased secretion of thyroid hormone. Another interpretation [12] has been suggested based on work reported by Loeser,[23] namely that the absence of thyrotropic substances from the body fluids of hyperthyroid patients might be due to an alteration or retention of the TSH by the overactive thyroid. Loeser injected 3000 units of TSH into intact rabbits and recovered the hormone from the blood for only one hour. However, he was able to demonstrate the hormone in the circulating blood of thyroidectomized rabbits treated in a similar manner for seven hours. Similarly Seidlin [24] recovered the hormone from the urine of thyroidectomized guinea pigs previously treated with large doses of TSH, but he was unable to demonstrate any thyrotropic activity in the urine of intact guinea pigs treated in a similar fashion.

In a previous publication [25] we reported that the thyroid stimulating hormone after being exposed by means of tissue culture technics to explanted adult rabbit thyroid tissues had lost its characteristic thyroid stimulating activity. Exposure to control tissues, except thymus and lymph nodes, did not diminish the activity of the thyroid stimulating hormone. We suggested that such findings might explain the reported absence of thyroid stimulating substances from the urine of patients with the thyrotoxicosis of Graves' disease.

The purpose of the present investigation has been to determine by means of tissue culture technics whether there is any difference in the effect of various types of human thyroid tissue on the activity of the thyroid stimulating hormone.

Methods. Human thyroids * removed at operation were used in this study. The toxic goiters were removed after the patients had received the usual preoperative treatment with rest and iodine. Small amounts of normal human thyroid tissue were obtained for this study by Dr. Oliver Cope at operations for parathyroid tumors. The non-toxic nodular thyroid tissue was obtained from routine operations for such goiters. For each experiment thyroid tissue weighing approximately 150 mg. was sliced and explanted in roller bottles [26] which had been coated with chicken plasma. A bathing fluid consisting of 15 c.c. of Tyrode's [27] solution, which contained the thyroid

* We wish to express our gratitude to surgeons of the Massachusetts General Hospital and of the Lahey Clinic for supplying us with fresh human thyroid tissue removed at operation.

stimulating hormone † in a concentration of one-half Junkmann-Schoeller [28] guinea pig unit per c.c. was added to each explant. The bottles were rotated 15 revolutions per hour in an incubator at 38° C. for 24 hours. Following such an exposure the medium was withdrawn and assayed for thyroid stimulating effect, in duplicate, on two one day old chicks, according to the microhistometric technic described by Starr and Rawson [29, 16] and by Rawson and Salter.[30] Two one day old chicks were each injected with one c.c. daily of the test medium for three days, and were autopsied on the fourth day. The thyroids were removed immediately and fixed in 10 per cent neutral formalin for 24 hours and then dehydrated in alcohol and embedded in paraffin. Sections were cut at 6 micra and stained with hematoxylin and eosin. Each section was examined under the oil immersion lens and inspected systematically from end to end in parallel pathways until 100 acini had been examined. Each acinus in the path of crossing which presented a definite wall, and was cut cross-sectionally, was included in the study. From each acinus one representative cell was chosen and its height determined by means of an ocular micrometer. Frequency curves were plotted from the observed measurements, and the mean acinar cell height of each examined thyroid was derived. To provide a standard measure of activity of the assayed media four groups of day old chicks were injected on three successive days with thyrotropic hormone in dilutions equivalent to ⅛, ¼, ½, and one unit. The mean acinar cell heights (MCH) of such test thyroids were determined as described above and compared with those of 10 control animals which had thyroid mean cell heights varying between 3.8 and 4.2 micra. The MCH of this group of thyroids averaged 4.0 micra. Four chicks treated with three daily injections of TSH in a concentration of ⅛ unit had thyroid mean cell heights which varied between 6.0 and 6.2 micra. The thyroid MCH of four chicks treated with ¼ unit daily for three days varied between 7.0 and 7.3 micra. These assays had an average MCH of 7.2 micra. Ten animals treated with ½ unit daily had thyroid mean cell heights which averaged 8.2 micra and varied between 7.8 and 8.3 micra. The average MCH of four animals treated with one unit daily was 9.0 micra and had a range between 8.8 and 9.2 micra (figure 1).

Results. Tissues from eight non-toxic nodular goiters were explanted and bathed in Tyrode's solution containing ½ unit of TSH per c.c. The basal metabolic rates of the donor patients before operation varied between minus 21 and minus 10. Assays of the bathing fluids showed no loss of thyrotropic activity. The mean cell heights of animals injected with media following exposure to these nodular goiters varied between 7.8 and 8.8 micra. The average MCH of this group of assay animals was 8.3 micra. Normal thyroid tissue from seven patients whose basal metabolic rates varied between minus 6 and plus 10 caused a loss of about one-half of the original thyrotropic activity in the bathing media which before exposure to these

† We are indebted to Dr. E. A. Sharp of Parke, Davis & Company for a generous supply of Antuitrin-T.

normal thyroids contained TSH in a concentration equivalent to ½ unit per c.c. The thyroid mean acinar cell height of 14 test animals treated with such media varied between 6.3 and 7.2 micra and averaged 6.8 micra. These thyroid mean cell heights are comparable to those of animals treated with ¼ unit of TSH daily in the standard response group studies.

Tissue from 20 thyroids removed from patients with Graves' disease was explanted and exposed in each experiment to 15 c.c. of Tyrode's solution containing TSH in a concentration equivalent to ½ unit per c.c. The period of exposure was 24 hours. Assays of these exposed media demonstrated a

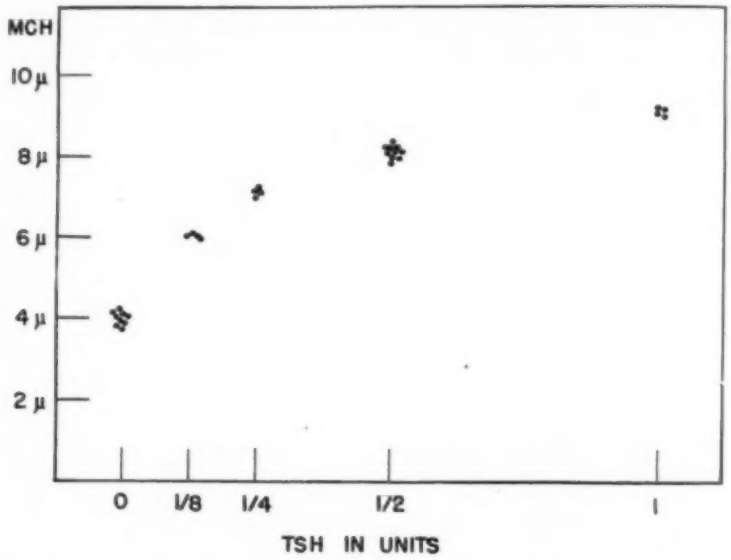

FIG. 1. Response of normal chick thyroid to increasing quantities of injected TSH. The ordinate shows mean cell heights, MCH, in micra, the abscissa the dose of TSH in Junkmann-Schoeller units.

loss of the major part of the TSH activity. The thyroid mean acinar cell height of 40 assay animals treated with these media following exposure to toxic thyroid tissue varied between 4.1 and 5.7 micra and averaged 4.5 micra.

Since it has been suggested that the apparent inactivation of the TSH here observed might be due to the interference of the normal TSH action on the test chicks' thyroids by some hormonal or metabolic substance washed out of the thyroid tissue slices and into the bathing medium, the following control studies were done. Two equal amounts of thyroid tissue from each of nine thyrotoxic patients were explanted into separate bottles. The medium added to one bottle contained TSH in a concentration equal to ½ unit per c.c. The medium in the corresponding bottle contained no pituitary hormone. At the end of the 24 hour exposure, TSH in a concentration equivalent to ½ unit per c.c. was added to the medium from the second

bottle, and both media were assayed in the usual manner. Assays of the media which contained the TSH during the period of exposure showed a loss of the normal TSH activity. When the hormone was added to the medium after exposure to the thyroid tissue slices there was no loss of TSH activity. The mean acinar cell heights of animals treated with the latter media averaged 8.1 micra (figure 2).

Two patients who presented clinical pictures of discrete toxic adenomata were seen during this period of study. Explants were made of the adenomatous processes as well as of the surrounding normal tissue, and the effect

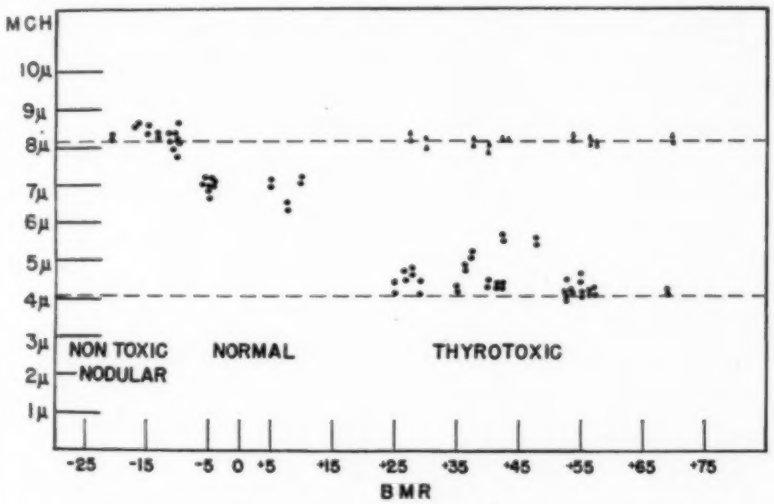

FIG. 2. Response of chick thyroid to injection of media containing TSH in the concentration of ½ Junkmann-Schoeller unit per c.c. after these had been exposed to human thyroid tissue (goiter) explants. Shown by dots. The ordinate discloses the mean cell heights, MCH, in micra, and the abscissa the BMR of the patient from whom the explanted material was derived. The left-hand flock of dots at the level of MCH 8 micra, and BMR −21 to −10, are for non-toxic nodular goiter cases. The next flock, MCH around 7 micra, and BMR −6 to +10, are for normal thyroids, and the right-hand flock, MCH from 4 to 5 micra, and BMR +25 to +65, are for toxic hyperplastic goiters. The black triangles show the thyroid MCH of chicks injected with TSH, ½ unit per c.c. which had been added to the medium only after the latter had been exposed to explants of toxic thyroid tissue. It is to be noted that no inactivation took place (see text). The lower horizontal broken line indicates the average thyroid MCH of ten untreated chicks; the upper, that of ten chicks treated with ½ unit of TSH.

of these tissues on the activity of the exposed thyroid stimulating hormone was determined.

One of these patients, Mrs. C., an Italian woman of 33, had noted an enlargement in the region of the left lobe of her thyroid seven years before, following a pelvic operation. This nodule increased in size gradually, but more rapidly in the three months just prior to admission. During the period of more rapid growth the patient noted some hoarseness and also some palpitation. She also complained of tremor of the hands. She had not noted any weight loss, but had had a marked increase in appetite. On

physical examination a 5 cm. rounded nodule in the upper portion of the left lobe of the thyroid was observed. This nodule was firm and non-tender. The hands were warm and tremulous when extended. The basal metabolic rate (BMR) was plus 24. Following two weeks on iodine there was no change in the BMR. At operation the thyroid adenoma, which after removal weighed 19 grams, was quite vascular and was removed completely. The right lobe was found to be pale and atrophic. A piece of the right lobe was removed for histologic examination and for in vitro studies. Eight days following the removal of the adenoma the BMR was minus one. The pulse rate which had been in the neighborhood of 100 to 120 fell to 70. Symptoms of palpitation disappeared and the patient admitted to being less nervous than before the operation. The adenomatous tissue when exposed to TSH containing medium, in tissue culture bottles, exerted an inactivating effect on the pituitary hormone. The apparently atrophic tissue found on the opposite side of the thyroid failed to inactivate any of the exposed TSH. The thyroid mean acinar cell heights of animals treated with media following exposure to the adenomatous and the atrophic tissue were 4.7 and 4.8 micra, and 8.0 and 8.5 micra respectively.

The second patient presenting a picture of toxic adenoma was a 23 year old white American born woman who entered the hospital complaining of nervousness and weakness. She had an intolerance to heat, and reported an increasing appetite with no loss of weight. She also complained of dyspnea and palpitation. On physical examination she was found to have a diffusely enlarged thyroid that did not transmit a bruit. She had prominence of the eyes with some lid lag, and was found to have a rapid and bounding pulse. Her basal metabolic rate was plus 24. She was instructed to take potassium iodide and was discharged on a medical régime. She did not make a good response to iodine. In the Out-patient Department her basal metabolic rates varied between plus 25 and plus 35. The left lobe of the thyroid gradually increased in size, and though the tissue on the right side of the trachea was palpable, it seemed definitely smaller and less involved than the tissue palpable on the left side. A left hemithyroidectomy was done and a biopsy was taken from the right lobe which at operation appeared to be normal except for two small nodules palpated deep in the central portion of the lobe near the trachea. Following the hemithyroidectomy the patient gained five kilograms in weight and had a marked improvement in symptoms. Her metabolic rate fell gradually to plus 2. Equal amounts of tissue from the removed adenoma and from the biopsied, apparently normal thyroid tissue, were explanted and exposed in parallel experiments to bathing media containing ½ unit of TSH per c.c. for 24 hours. Thyroid mean acinar cell heights of test animals treated with medium after its exposure to the adenomatous tissue were found to be 4.1 and 4.3 micra indicating an almost complete inactivation of TSH. Media following exposure to the apparently normal tissue contained about one-half of the original TSH activity, thus in-

activating about the same amount of TSH as normal thyroids were observed to have done. The mean acinar cell heights of such assay thyroids were 7.1 and 7.1 micra.

Discussion

These findings indicate that normal human thyroid tissue can inactivate its stimulator, the thyrotropic hormone, when the latter is exposed to the thyroid tissue in vitro. This inactivating effect of normal human thyroid tissue on TSH is similar to that observed in comparable in vitro studies on the effect of rabbit thyroid tissue on the activity of TSH. In terms of tissue weight, however, the normal human thyroid does not inactivate the same quantity of hormone as does the rabbit thyroid. This difference can probably be explained as a variance in species response. Dr. Ruth E. Cortell, working in our laboratory, has observed in studies on tissue respiration with Warburg technics that the oxygen consumption of thyroid tissue varies from one species to another. She has also observed that the human thyroid has a much lower rate of oxygen consumption than that of any animal thyroids studied.

The observation of variations in the amount of hormone inactivated by pathologic human thyroid tissue as compared to the amount of hormone altered by normal human thyroid tissue is probably of real significance in considering the pathologic physiology of thyroid disease. The observed failure of the non-toxic nodular thyroid tissue to inactivate its stimulator may provide an explanation for the low basal metabolic rates so frequently observed in many non-toxic goiterous patients. Conversely the observed increased ability of thyroid tissue removed from people suffering from Graves' disease to inactivate the thyroid stimulating hormone may point to an increased sensitivity of such diseased thyroid tissue to normal, or possibly increased amounts, of the pituitary secreted thyroid stimulator. On the basis of these observations one might advance the hypothesis that thyroid function is, at least in part, dependent upon the ability of the end organ to respond to its stimulator. The varying effects of normal and pathologic thyroids on the TSH may well direct our attention in endocrine research to studies of the end organs and their responses to various hormonal actions. It seems plausible that various endocrinopathies may be on the basis of abnormal responses of the end organs to hormonal actions as well as on the basis of abnormal amounts of secreted hormones. Indeed the varying effects observed of toxic adenomatous tissue and non-diseased tissue taken from the same thyroid glands, on the activity of the exposed TSH in parallel experiments, suggests that certain abnormal states may be dependent upon the reactivity of localized cellular groups. Lein [31] has reported observations that likewise indicate variations in the metabolism of various types of thyroid tissue. He reported that toxic thyroid tissue when subjected to oxygen consumption studies in the Warburg tissue respirometer had a greater QO_2 than

normal or non-toxic goiterous tissue. He also found that the latter tissue consumed oxygen at a slower rate than did normal tissue.

Since we have observed in this study that thyroid tissue removed from patients with thyrotoxicosis inactivates nearly twice as much TSH as does normal human thyroid tissue, it seems quite possible that the reason for our inability to demonstrate with present methods any thyroid stimulators in the urine of thyrotoxic patients might be due to the complete inactivation of the secreted TSH by the overactive thyroid.

To explain the reaction as described is difficult with our present limited knowledge of cellular physiology and chemistry. Since bathing media containing no pituitary hormone, after 24 hour exposures to tissue slices of toxic thyroids, did not inhibit the action of TSH added to the media following removal from the tissue cultures, it seems unlikely that the observed inactivation of the exposed thyrotropic hormone was on the basis of inhibition by thyroid hormonal substances washed out of the tissue slices. Another possible mechanism of such an inactivation of the hormone is that of an enzymatic oxidative reaction. Investigations are now in progress in our laboratory to determine whether such phenomena exist in the pituitary thyroid axis.

Summary

1. Observations have been made on the effect of normal and pathologic human thyroid tissues upon the activity of pituitary thyroid-stimulating hormone exposed to them by means of tissue culture technics (explants).

2. It was observed that the thyroid stimulating effect of a pituitary extract is significantly diminished following its exposure to normal human thyroid tissue.

3. Non-toxic goiterous tissue explants were observed to exert no effect on the activity of the TSH exposed to them.

4. Tissue slices taken from thyroids of patients with Graves' disease were found to inactivate about twice as much TSH as equal amounts of normal human thyroid tissue.

5. The hypothesis is advanced that the observed absence of thyrotropic hormone from the urine of thyrotoxic patients is due to the complete inactivation of TSH by the overactive thyroid of Graves' disease.

6. It is suggested that investigations in endocrine physiology, both normal and morbid, should include consideration of the state of the end organs in interpreting hormonal responses.

We are indebted to Dr. J. H. Means for his valuable and stimulating advice in carrying out these studies.

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PERSONNEL SELECTION: A SHORT METHOD FOR SELECTION OF COMBAT OFFICERS*

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For the past four years the Grant Study of the Hygiene Department at Harvard has been engaged in investigations concerning healthy, normal young men. In these investigations the technic of the fields of medicine, anthropology, physiology, social studies, psychology and psychiatry were employed, and the procedure by which the different technics were all applied to the same young men was essentially coöperative. Detailed information of wide scope was obtained on about 270 young college men who were unselected save for health and "normality." A simple system of classifying personality traits of normal persons was developed by which, to a certain degree, a diagnosis of the "normal" was attainable.

The classification of persons as "normal" does not need to be based only on the absence of disease. For example, one simple way of characterizing a "normal" person is by stating what he can do. Indeed, the original meaning of the word "person" is "the part which he must play." Moreover, there are no insurmountable difficulties in finding out what people can do, so that methods of exploring potentialities of people can be rather easily developed. This approach to the study of people avoids the usual method of searching for disease or potential disease, psychopathology or potential psychopathology, although such disabilities inevitably emerge from procedures of this nature.

In the past year this study has been focused particularly on aids in the selection of personnel for various occupations. It is our purpose to summarize, as an example, a short method for selection of combat officers to which most of our time recently has been devoted.[1] Variations of the method can be applied to the selection of non-combat officers and candidates for civilian trades. Emphasis has been placed on having a method as short as is consistent with reasonable accuracy and one which can be used in addition to present methods. It is assumed that preliminary medical examination, mental tests and other data have been obtained. Many details of a complete personality study have been eliminated.

A combat officer should be physically fit, have certain personality qualities for leadership and a physique which will give him presence and enable him to withstand hardship. This method combines these three qualities in three tests which are as follows:

(1) An eight minute test of physical fitness, which gives an accurate measure of the ability of the man to withstand hard muscular work and

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From The Grant Study, Hygiene Department, Harvard University. The details of the method have been published in a booklet.[1]

enables him to be grouped as excellent, good, average or poor in physical fitness.

(2) A 10 minute interview devoted to the study of the personality and activities, which permits classification of the man as excellent, acceptable, doubtful or poor officer material.

(3) A brief inspection of the body build to determine characteristics of masculinity which have been found to be related to physical fitness and combat officer fitness.

The test for physical fitness has been applied to over 8,000 college students, large groups of Naval Aviation Cadets, a group of Commandos in England and many high-school boys and college girls. It has been introduced in the Navy and Army Aviation training programs. Initial studies with the short interview method were made on members of the Army R.O.T.C. for whom a rating based on at least two years' performance was available. There was good agreement, ranging from 93 to 100 per cent between the rating made by the short interview and that given by the Army officers. Subsequently, the test has been applied to other classes of the Army and Naval Reserve Officer Training Corps, candidates for the Army Enlisted Reserve Corps at Harvard College, and applicants for commissions at the Office of Naval Officer Procurement of the First Naval District. Well over 2,000 interviews have been performed. Estimates of body build have been made on many thousands of college students and others.

I. A Short Method of Estimating Physical Fitness: The Step Test. The test for estimating physical fitness has evolved out of many years of continued research by many workers at the Harvard Fatigue Laboratory. It is a simplification of more elaborate technics which have included measurements of heart rate, blood pressure, pulmonary ventilation, oxygen consumption, blood sugar and lactate variations in relation to degrees of work usually performed on a motor-driven treadmill. Many complicated technics can be eliminated for practical purposes and satisfactory estimation of a man's fitness for hard work can be made by exposing him to a simple standard form of exhausting exercise and taking into account two factors: the length of time the exercise can be sustained and the speed of recovery of the heart rate upon completion of the exercise. This simplification of method has been the result of recent work, particularly by R. E. Johnson, L. Brouha and R. C. Darling.[2, 3, 4]

The simplified test for physical fitness under consideration is called the "Step Test" and is performed as follows: the subject steps up and down a 20 inch platform 30 times a minute for five minutes or until he has to stop from exhaustion. An observer counts the time as in military marching as follows: "*Up*—2—3—4, *Up*—2—3—4," the "*up*" coming every two seconds. The subject then is seated and his pulse is counted from 1 to 1½, 2 to 2½, and 3 to 3½ minutes after the exercise is discontinued. The score, or index of physical fitness is computed by dividing the duration of exercise

in seconds by twice the sum of half-minute pulses in recovery ($\times$ 100). As many men can take the test at one time as there are observers to count pulses.

The meaning of the figure thus obtained has been found in healthy young men to be as follows:

Below 55 = Poor physical condition
From 55 to 64 = Low average
From 65 to 79 = High average
From 80 to 89 = Good
Above 90 = Excellent

Figures 1 and 2 show the distribution of scores in college freshmen before and after conditioning and in a commando unit.

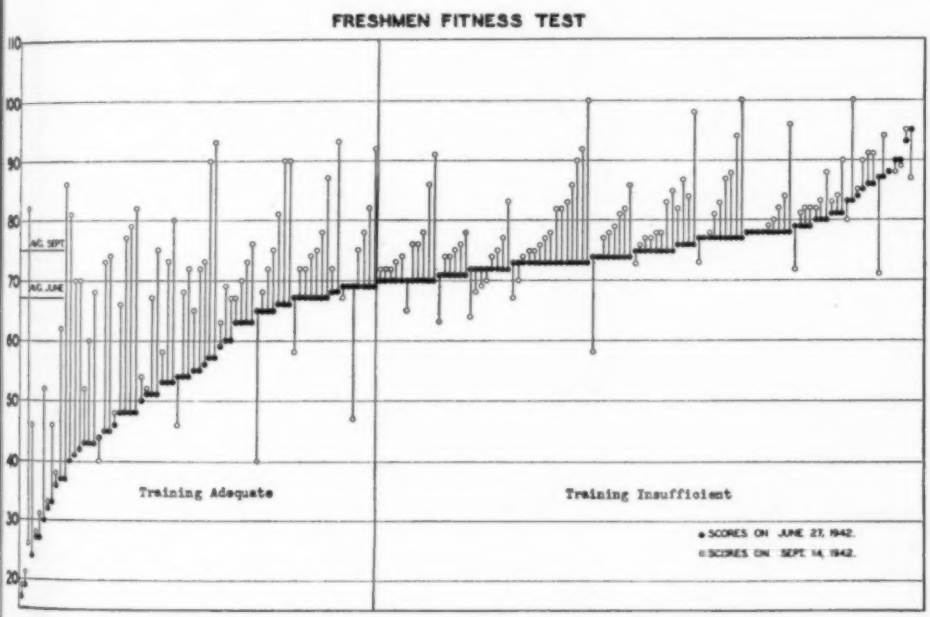


FIG. 1. The physical fitness index in a sample of the freshman class at Harvard. The black dots represent the scores for physical fitness on entrance before the course of physical training. The white dots are the scores of these men after 10 weeks of physical training. The average score before training of this group was 67; after training 75. The men less physically fit gained more than those more fit, showing that the training was not severe enough for the fit men. Those that scored less on the second trial had ill health or for some reason did not take the training. Varsity athletes in training score as a rule above 90. The best record was 180, made by the stroke of the Varsity crew.

This test measures general physical fitness independent of any particular strength or skill. It utilizes large muscle groups, places the cardiovascular and respiratory systems under definite stress and takes into account ability to recover from exertion. The scores have little relationship to those obtained with the Schneider, the McCloy, or the McCurdy-Larson tests which may be useful in detecting various failures of the cardiac and circulatory mechanisms, but are not always reliable for evaluating fitness for hard work

in healthy individuals. It is not necessary to take into account the pulse rate before the exercise because this has been found to have almost no relationship to physical fitness in healthy subjects.* The pulse rate at rest may be extraordinarily low in certain athletes who have been in training for years, but in general the pulse rate at rest is no indication of physical fitness in healthy young men. Emotional factors may increase greatly the pulse before exercise or before the medical examination, and this has been found to occur in both the physically fit and the physically unfit.[5]

When the test is applied to men who have been leading sedentary lives, it will probably not distinguish between those who will respond well to physi-

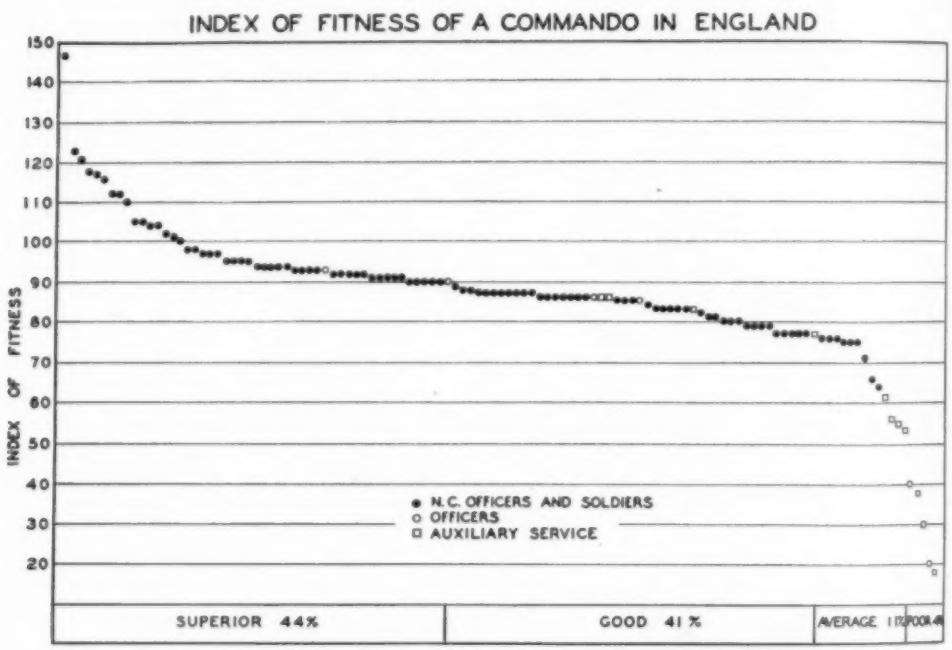


FIG. 2. The dots are the scores of individuals in a Commando unit in England. The average score was 90, which is comparable to that of Varsity athletes in training. The men with low scores should be eliminated from the group as they will hold back the better men.

cal training and those who will not. It will help to differentiate homogeneous groups of men for physical training or combat work, so that the progress of the whole group will not be held down to that of the poorest, and it will assist coaches and others having to do with the physical training of men.

II. A Short Interview for the Selection of Combat Officers. Dr. William Woods has been particularly responsible for the development of this short interview method for selection of combat officers. The approach is clinical and the task is to judge by personality traits whether a man is to be

* Data at hand, however, indicate that pulse rate taken under standard conditions may be related to personality traits and possibly to certain constitutional traits.

judged excellent or good (A), acceptable (B), questionable or doubtful (C), or poor (D) officer material. The time is limited to 10 minutes only. The examination is different from the ordinary psychiatric examination which attempts to weed out unsound individuals or those who betray manifestations of psychoneurosis, mood disorders, and intellectual inadequacy. The assumption is that such individuals have already been eliminated and that we are dealing with essentially healthy and normal young men. Nevertheless,

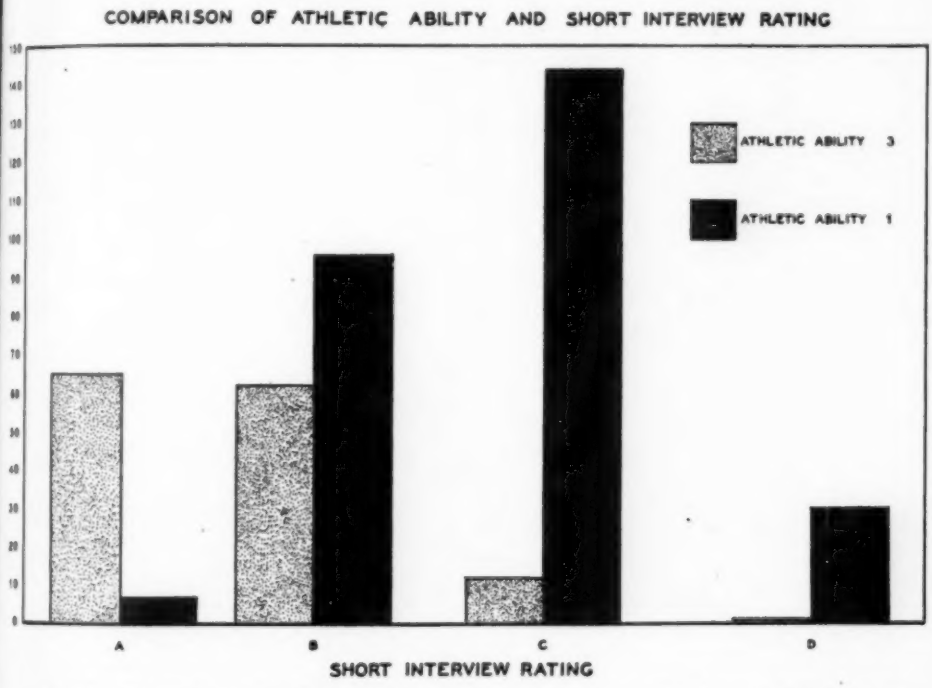


FIG. 3. Comparison of athletic ability and short interview rating for combat officership (420 candidates). In the short interview, athletic ability is rated 3 if the candidate engaged successfully in major sports, particularly contact sports like football, hockey and boxing, and if sport was a major interest. It was rated 2 if the candidate's interest was less than this and 1 if he lacked competitive spirit and avoided contact sports. The high rating for athletic ability, shown here by the dotted columns, was particularly prominent in those rated A or B for combat officership in the short interview. Those rated low for combat officership (C and D) as a rule had low ratings also for athletic ability. A similar correlation could be shown also between combat officer ratings and such traits as "strong," "alert," "dependable," etc.

instabilities of character if present are apt to appear because of the very nature of the interview.

The interview is conducted in privacy, upon a spontaneous, informal plane, and although a uniform field of facts is covered, it is kept flexible. A summary sheet is provided for checking of traits, but little writing is done during the interview.

Throughout the interview, the appearance and expression of the candidate

are under observation. It is unnecessary here to go into detail about the qualities or traits which are looked for in an officer candidate. The first impression is usually a very valid one. One is asked to judge whether the appearance of the candidate is strong or weak, inspiring or unimpressive, alert or dreamy, etc. Under this heading comes the speech which is an important

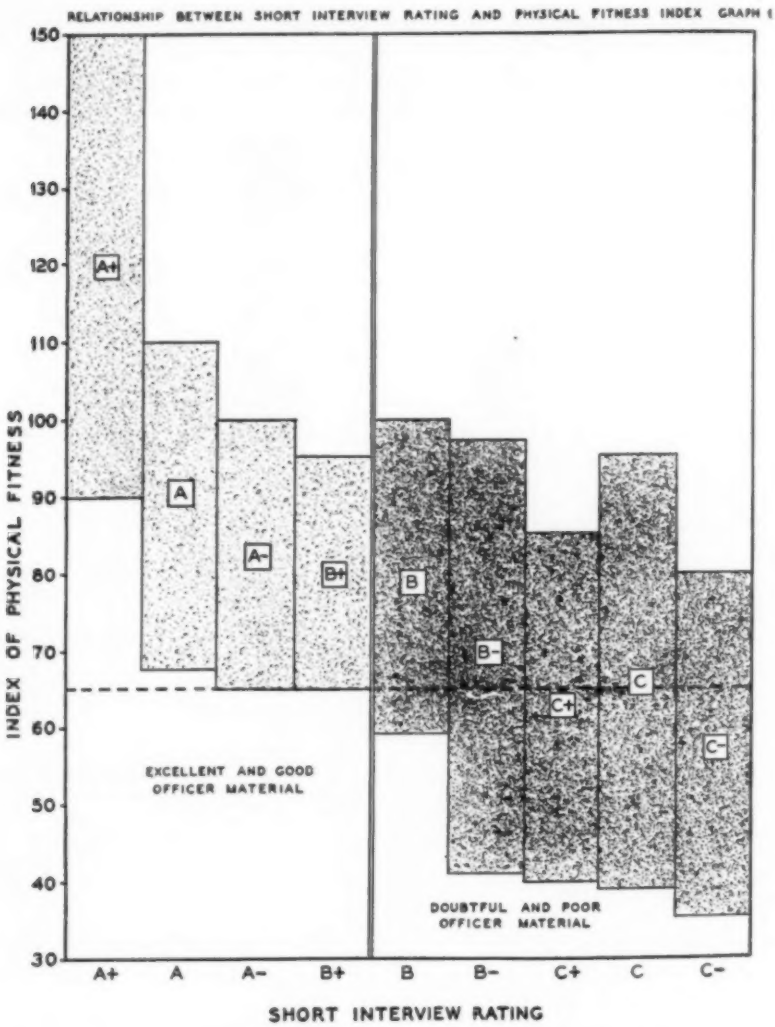


FIG. 4. Relationship between short interview rating and physical fitness index. This chart shows the range of physical fitness scores of candidates variously rated by short interview for combat officership. No individual considered excellent or good officer material scores less than 65. There is a strong tendency for those rated high for combat officership to score high in physical fitness, and for those rated low in combat officership to score lower in physical fitness. However, one does find a number of men who may score well in physical fitness who rated low in combat officership. This is because these men may have lacked other qualities of personality which would permit them to be considered first-rate officers.

consideration for an officer: is it clear or indistinct, fluent or halting, full or thin?

The manner of questioning the candidate during the interview deserves special comment. It should be borne in mind that the candidate, not the interviewer, should do most of the talking. Therefore, all questions should be brief, rather general and should give the candidate an opportunity to expand. Examples of questions are as follows:

In the case of a college student:

"What field do you major in?"

"How did you happen to choose that field?"

In the case of the non-college man:

"What was your work?"

"How did you get into it?"

And for all men:

"What would you like to do for career, or life work?"

"Do you like athletics?"

"What is your favorite sport?"

"Do you like out-door life?"

"Are you handy with tools?"

"What do you do in your spare time?"

It is evident that the manner in which an answer is given rather than the actual content of the answer contains the important clues to the character of the candidate. The actual occupation of the candidate affords a natural opening and this leads to choices of career and attitudes to military service. Then various activities, special skills, hobbies and accomplishments can be discussed. Lastly, social traits, health, emotional traits can then be brought out in an orderly way.

At the end of the interview, an over-all rating is given, as to whether the candidate in respect to combat officer fitness is excellent or good (A), acceptable (B), questionable or doubtful (C), or poor (D). This rating scheme can profitably be further divided. A summary sheet may then be filled out which requires checking various traits. This serves as a record, a check on the interviewer and as a basis for research.

The short interview is best given by men, preferably physicians, who have had experience in dealing with people and have some native ability for "sizing up" people. A short period of practical instruction is desirable, where actual interviews are conducted in the presence of an experienced interviewer. It is remarkable how soon and how well two people can come to identical agreement about the majority of candidates.

Figures 3 and 4 illustrate important relationships between interview findings and athletic ability and physical fitness.

III. The "Masculine Component" in the Selection of Combat Officers. The determination of masculine component and its relationship to combat officership has been the result of work by Dr. Carl Seltzer.[6] It has been

selected from many other anthropological characteristics of body build which are related to combat leadership, but it is the simplest and quickest to determine.

It is a common observation that the male body build varies from the strong, rugged, well-muscled, angular, masculine type toward the softer, rounder, less muscled, feminine type. This is true even within the normal range of men in which one does not suspect actual endocrine abnormalities. Figures 5 and 6 illustrate the anatomical characteristics which are observed in making a judgment of strong, as opposed to weak masculine components. It will be seen how intermediate degrees (medium or very weak) of masculine component can also be distinguished profitably. A four-fold scale comprising strong, medium, weak and very weak masculine component is useful.

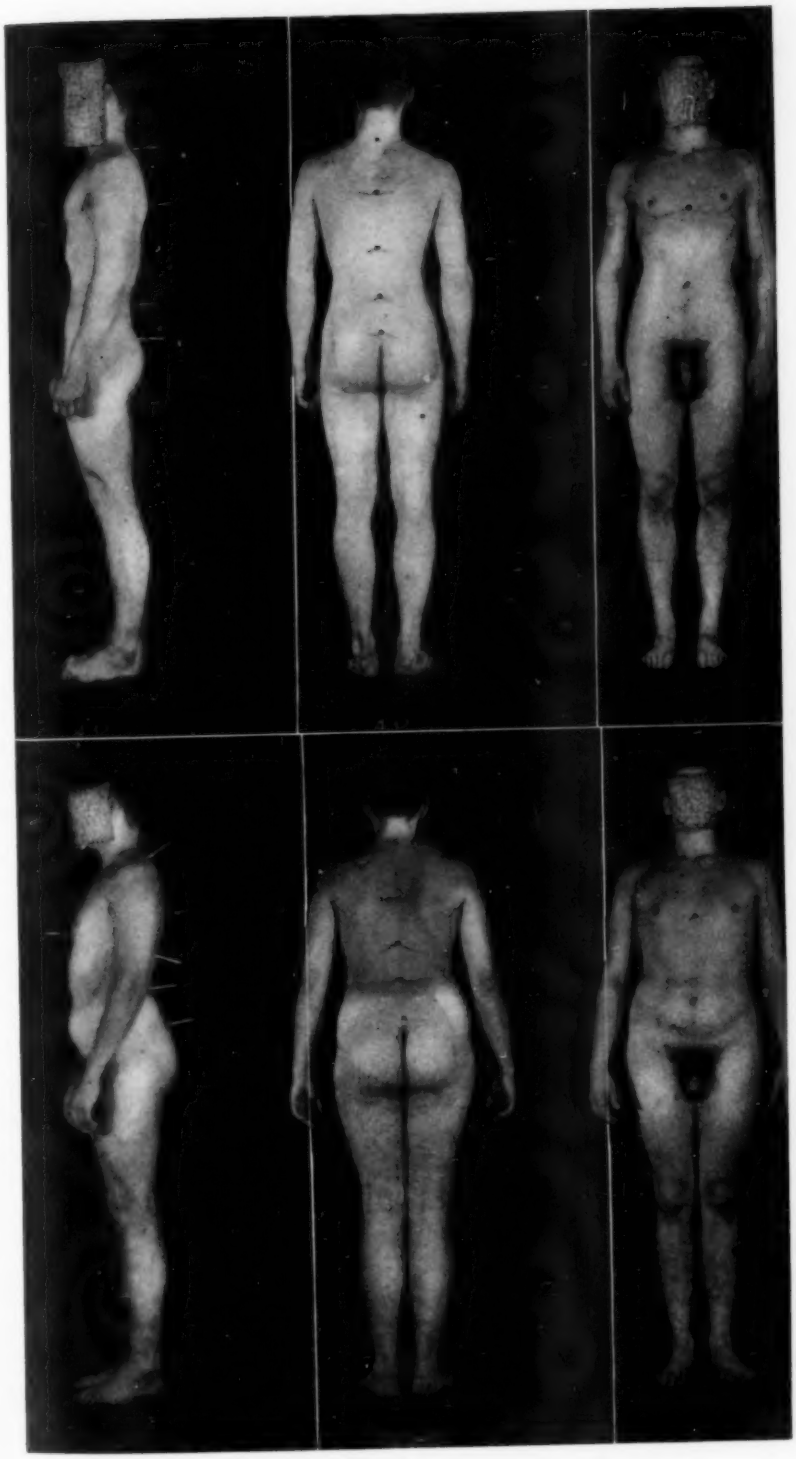
Figures 7 and 8 illustrate the relation which exists between the masculine component of body build and (1) the physical fitness of individuals as determined by the Step Test; (2) the combat officer qualities of candidates for officer training. The estimate of masculinity can thus be a useful adjunct in the selection of combat officers.[6] Individuals who are weak in masculine component are on the whole deficient in combat officership qualities and inferior in physical fitness even after training.

Discussion

From the particular example, selection of combat officers, it may be seen how different tests may be employed and the interview altered when the task is to select personnel for other occupations. A few simple basic principles for successful selection of personnel may be stated. First, there must be knowledge of ranges of traits and characteristics of people from whom the selection is to be made. Second, there must be knowledge of the particular kinds of traits and characteristics requisite to the particular task. What are the men like who have been successful in it? What are the men like who have been unsuccessful? Knowing what to look for and how to look for it is the essence of the problem. There should be recognition of the fact that "normal" people vary greatly one from another and yet remain within the range of "normal." It is appropriate, of course, to eliminate the medically

Fig. 5. (*Above*) Young man judged to have strong masculine component in body build. Note: (1) general angularity and ruggedness of body outline and good muscularity; (2) relatively narrow hips to shoulder breadth; (3) flatness of mammary area; (4) flatness of abdominal area; (5) interspace between thighs; (6) prominence of inner curvature of calves; (7) pubic hair running towards navel. In making actual judgments these are also observed: lack of hyperextensibility of elbows and good muscle tonus.

Fig. 6. (*Below*) Young man judged to have weak masculine component, but well within "normal" range. Note: (1) roundness and softness of body outline, without prominent musculature; (2) relatively greater hip breadth to shoulder breadth; (3) fullness in mammary area; (4) feminine abdominal protuberance; (5) approximation of thighs; (6) greater outer curvature of calves; (7) lateral distribution of pubic hair. In making actual judgments there are to be observed also the arms carried with an angle at the elbow (hyperextensibility), and poor muscle tonus.



unfit, but the work of selection has not been completed until there have been distinguished among the medically fit those whose traits are adapted to the task at hand.

There is a great need for better diagnosis of people. Tests of many

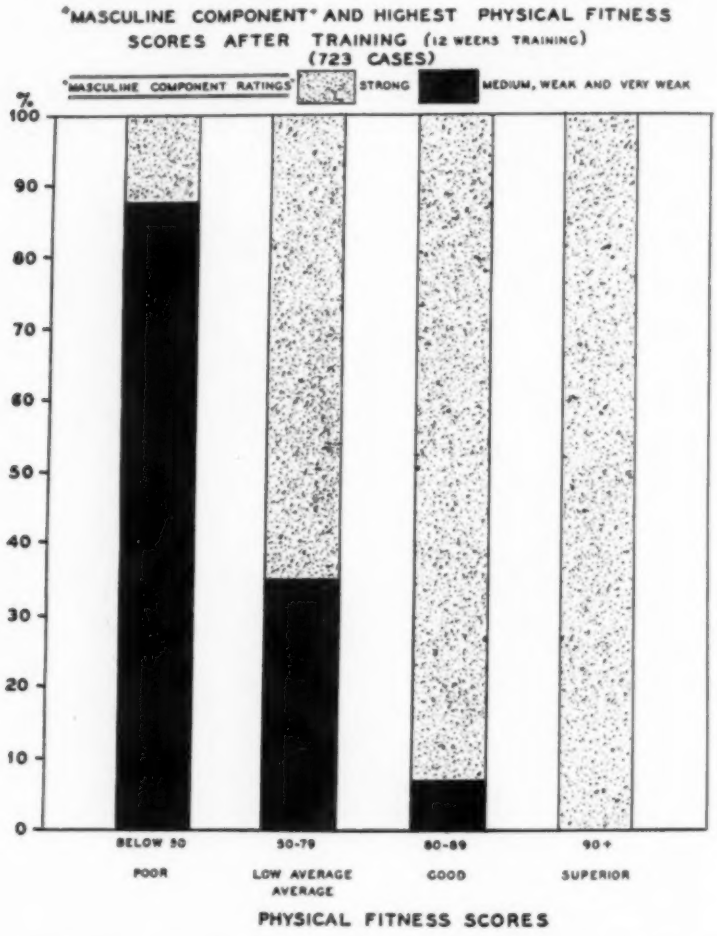


FIG. 7. "Masculine component" and highest physical fitness scores (723 cases). The light part of the columns represents the per cent of candidates having strong masculine component; the black parts of the column those having medium, weak or very weak masculine component. All of those scoring over 90 for physical fitness had "strong masculine component" and 93% of those scoring 80–89. Weaker masculine component was prominent in those scoring less in physical fitness.

kinds have been developed, but no test as yet can take the place of seeing and talking to the individual. Subjective feeling about an individual, allied to that of the physician when he makes a medical diagnosis is still necessary. But the physician's diagnosis, subjective or intuitive though it may be, is based on years of experience with patients and is ultimately factual,

although the facts and factors are too complex to yield to mathematical analysis. As progress is made, however, and tests develop, there is less necessity for subjective diagnosis. The procedure in the "diagnosis" of normal personalities seems to be the same, and as knowledge advances, it may become

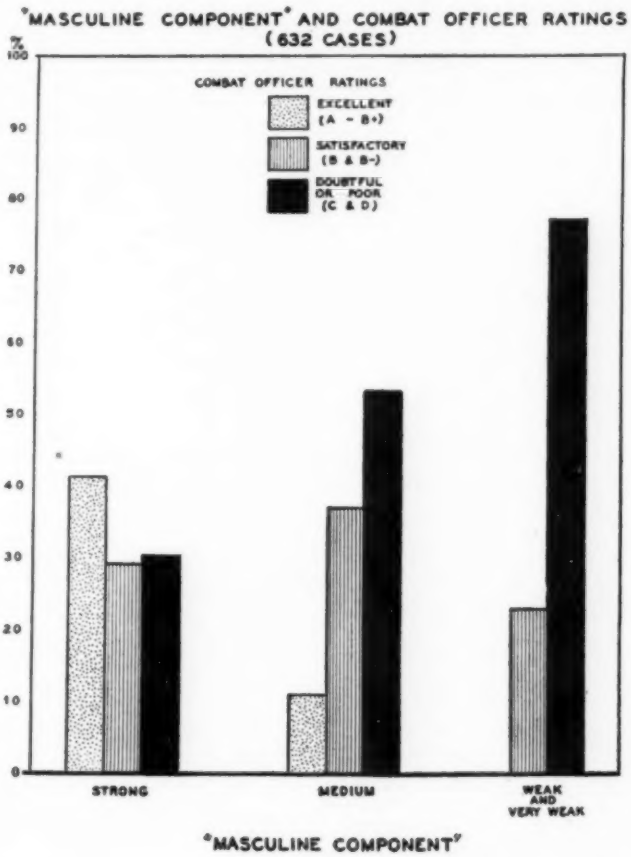


FIG. 8. "Masculine component" and combat officer ratings (632 cases). This chart shows the relationship between masculine component and combat officer ratings. The combat officer ratings were made by army or navy officers in charge of the R.O.T.C. In the first group with "strong masculine component" 41 per cent were rated as excellent officer candidates. In the group with "medium masculine component" only 11 per cent were rated as excellent officer candidates, 54 per cent as doubtful or poor. Of the group with "weak or very weak masculine component" no men were rated excellent for combat officership, 77 per cent were rated doubtful or poor.

not too difficult to assign people accurately to appropriate training for particular tasks, careers and occupations.

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POST-CONCUSSION SYNDROME—A CRITIQUE*

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THOUGH head injuries are usually considered to be the province of the surgeon, the physician, as Richard Bright [1] remarked over a century ago, is so commonly called upon to alleviate their after-effects and has so often to take them into account in relation to general disease, that it behooves him to interest himself in their mechanism.

Traumatic disorder of the nervous system is in general of a kind that is at its worst immediately following the injury, and thenceforth lessens in severity as reparation is made. This is true of the paralysis due to damage to the cerebral cortex, to injuries of the cranial nerves, and to such hemorrhage as may be directly provoked. There are, it is true, some immediate complications in the first few days, such as epidural hemorrhage, acute subdural hematoma, and meningitis, which appear as separate entities after the event. These, however, are the true surgical anxieties and are little the physicians' concern.

By the time the patient is referred to the physician he is usually beyond the stage of these immediate surgical hazards, and the first questions that arise in the mind of the physician are somewhat as follows. Is the patient's present trouble the residue of some greater disorder precipitated by the head injury? Or is it something developing afresh, and if so, is it due to the trauma or to some unrelated disease? Let us list the chief general cerebral disorders which occur in the convalescent period after head injury.

GROUP I

Disorders which are maximal in degree immediately after head injury and tend to progressive improvement

Paralysis
Intellectual impairment (stupor, confusion)
Headache (local, usually occipital, worse on movement)
Vertigo

GROUP II

Disorders which appear at an interval of weeks and tend to increase in severity

Epilepsy
Stupor, hemiplegia (chronic subdural hematoma)
Bouts of headache, dizziness, loss of concentration ("post-concussion syndrome")
Psychoneurosis

One of the commonest after effects of head injury is the "post-concussion syndrome," and I have put it unhesitatingly in the second group. Its place here is little recognized; in fact, much of the confusion surrounding the sub-

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ject is derived from lack of appreciation of the delay in onset. It does not appear until the patient is fit to attempt mental and physical exertion, and its periodic nature is then related to attempted exertion. The syndrome has acquired a large literature since attention was first drawn to it in surgical writings (Hutchinson, 1877).[3] It has been reviewed by Symonds,[4, 5] Strauss and Savitsky,[8] Schilder,[9] Russell,[10] and Schaller [11] in recent years.

The bouts of throbbing, sometimes piercing ache are usually of brief duration, and are localized diffusely to alternate sides of the head. They are precipitated by effort, both physical and mental, and when present the headache is markedly influenced by posture. It is associated with dizziness of a non-specific, vague, rocking kind, and with difficulty in mental concentration. There is often insomnia and depression with emotional lability. When these latter emotional symptoms are associated with a constant dull pressing sensation in the head instead of the bouts described above the condition is more clearly a psychoneurotic depression and not the true post-concussion syndrome. All investigators have remarked on the relative constancy of the more characteristic symptoms in patients who have had no opportunity for collaboration, a constancy which tends to indicate some identity of mechanism of symptom production. All authors are agreed on the psychoneurotic aspect of the reaction, yet almost all have seen it follow severe head injury in a stable personality sufficiently often to feel that some organic basis is possible. A large number of clinical tests have at various times been advocated as objective criteria of the condition. None, however, has stood the test of time (see Strauss and Savitsky [8]).

It has been noted by many that patients who suffer severe lacerations of the brain often fail to develop the characteristic syndrome. I have indicated elsewhere,[15] however, that it tends to develop late in these patients, a fact more obvious to the neurologist and physician than to the surgeon.

A number of contradictory statements in the literature arise from confusion of types of headache and circumstances of origin of the syndrome. It is necessary to point to some obvious discrepancies. A recent paper by Malone [2] claims relief for the post-concussion syndrome by treatment with prostigmine. This investigator summarizes the effect of this drug in a table of 10 cases. Two cases are singled out for mention in greater detail. The first is that of a 40 year old male who had suffered a head injury two years previously and had since had attacks of "dizzy spells," each of which necessitated bed rest for two or three days. He did not suffer from headache. Such prolonged attacks are not a usual post-concussional symptom and more closely resemble Ménière's syndrome. The second case reported in detail was a housewife, aged 59, who sustained a head injury in January 31, 1940, since which time she had suffered from "frontal and occipital headaches, photophobia, almost constant dizziness, and occasional diplopia." The condition persisted until February 22, though she had remained in bed. Institution of prostigmine treatment was then accompanied by subsidence of the symptoms, so that by March 3 the patient was able to be about. In Sep-

tember she had had further symptoms. This type of headache and dizziness is that present in almost all cases of moderate head injury (see Group I) and particularly in patients who have had traumatic subarachnoid hemorrhage. Its natural course is a gradual subsidence in some two to six weeks depending upon its severity. The subsidence in just over four weeks in Malone's case is, therefore, not particularly surprising. But to advance such a condition as the post-concussion syndrome is wholly confusing. That point of view is not at all an uncommon one.

There are two views which have wide support at the present time. One is derived from the investigations of Penfield,[16] who claimed that he had demonstrated subdural adhesions in patients with post-traumatic headache; the other is exemplified by the view of Russel who is quoted [13] as saying: "Whereas in the last war the soldier who cannot 'stand the gaff' considered himself a victim of 'shell shock' and might well show hysterical phenomena, paralyses or anesthesias; in this war he has learned that the complaint of headache following a blow on the head is apt to serve as entitlement to invalidism and discharge." The first explanation, Penfield's, throws all the emphasis on the scar. The second implies that all is self-motivated.

In my own experience with a large number of military cases as well as the usual neurologist's experience with civilian cases, neither of these views meets the facts. Patients with subdural scars seldom have headache and this headache is then localized to the region concerned. The Penfield and Norcross [12] test of the presence of subdural air following lumbar insufflation is positive in many patients without head injury, as demonstrated conclusively by Lemere and Barnacle.[14] On the other hand a post-concussion syndrome following very severe head injury can often be related to impaired intellectual capacity.[15] The syndrome is then a reaction which occurs whenever the patient attempts something beyond the limit of his powers of cerebration. The difficulty here is that such impairment can be conclusively demonstrated only by well conducted intelligence tests, though any simple appraisal of memory and judgment should suffice for clinical purposes.

The post-concussion syndrome can also occur as a pure psychoneurosis following trivial head injury, but the mechanism is seldom one of malingering. Careful history taking reveals most commonly that the patient has had previous liability to neurosis, and that some stress or exhaustion preceding the head injury had primed the occurrence of another psychoneurotic manifestation (Denny-Brown [15]). Next in order of frequency as underlying cause of a psychoneurotic type of post-concussion syndrome following head injury is the addition of undue physical or mental stress in the weeks following head injury. The man who breaks down on too early return to work or duty comes under this category, and the reaction may be in no way attributable to failure on his part. The basic defect is then "organic." Thus, whatever the mechanism of production of these symptoms which make up the syndrome, the underlying failure may be psychoneurotic or an organic remainder from the injury or a combination of the two.

It is, therefore, concluded that the post-concussion syndrome is a reaction to circumstance and, as such, appears as a separate event at an interval after injury. Thus, it has to be distinguished chiefly from epilepsy and from chronic subdural hematoma. The stupor and increasing paralysis due to the latter should be sufficiently distinct to avoid confusion. In rare cases a subdural hematoma is the cause of the mental inadequacy which leads to the syndrome. Secondly, it is emphasized that the underlying cause may be any or all of three factors—severe general damage to the brain leaving intellectual impairment, constitutional liability to psychoneurotic reactions, and undue physical or mental stress in the post-traumatic period.

Careful history taking will resolve the importance of these factors in the individual case. It is found that physicians are chiefly troubled by the definition of intellectual impairment. However, if it is remembered that this is one of the features that belong to the Group I mentioned earlier, and that, therefore, it is derived from some greater disorder immediately following the injury, the indications should be clear. It is the patient who has been unconscious for a long period, confused and disoriented for many days or weeks, who is found later to suffer intellectual impairment, never the man who was unconscious for only minutes or hours. A reliable history of the injury will, therefore, either rule out or indicate this possibility.

Special procedures such as electroencephalography and air encephalography are of great value in demonstrating localized atrophy and the focus of epilepsy. They have been of little value in the differential diagnosis of the post-concussion syndrome because the changes, if any, are slight in such cases, are not greater than is present in many normal people who have never had a head injury, and even when known to follow head injury are not consistently associated with symptoms. The milder changes demonstrated by these methods do not form a disability unless supported by other evidence (Denny-Brown [15]).

It may be of topical interest to record here that all the cases of post-concussion syndrome following close exposure to the blast of bomb or shell seen by me followed an initial psychoneurotic disturbance, without brain damage. Conversely, two patients within 12 feet of the burst of large bombs were not concussed, though receiving other brain injury from splinters for which they came under our care. They did not suffer from the syndrome.

The effectiveness of treatment of the post-concussion syndrome depends on accurate assessment of its underlying cause or causes. The success achieved in a British hospital for military and R. A. F. head injuries, with which the author was associated for its first 18 months, may be judged from figures published by Symonds [6] from a follow-up of the first 1,000 cases. These patients on admission to the hospital were suffering from disability lasting six weeks or more after a head injury. There were 871 men on whom a long period follow-up was possible. Sixty-seven per cent were returned to active service duty successfully (i.e., maintained satisfactory duty for a period of months). A severe psychoneurotic type of disorder was

found to be as refractory to treatment as a severe organic disorder, but psychoneurotic factors in men of stable personality responded well to treatment.[15, 7] A test of heavy exercise, for example digging or sawing wood, is an absolute necessity before final discharge from hospital to duty if relapse is to be avoided.

The type of disorder most difficult to treat is lowering of intellectual capacity, though much can be accomplished by adjusting such patients' occupation so as to bring it within their cerebral limitation. Within the armed forces such adjustment can be accomplished only if the ultimate defect is small. It is, therefore, of the greatest importance to make early and reliable estimation of prognosis in this respect. A valuable criterion is the duration of post-traumatic amnesia, i.e., the duration of time from the injury to the patient's first current memory of later events. Though the time interval is based on subjective evidence, it can be checked against records of his state in the relevant period which should have shown coma progressing to confusion and disorientation with lack of insight. The correlation of duration of post-traumatic amnesia (P. T. A.) is well brought out in Symonds' analysis [6] of follow-up cases. When the P. T. A. was less than one hour the percentage of successful return to duty was 77. For P. T. A. of between one and seven days 62 per cent returned. Following a P. T. A. of more than one week only 52 per cent returned. The chief disabilities due to laceration, namely epilepsy or paralysis (including cranial nerve palsies) have little or no correlation with duration of amnesia, for in penetrating war wounds loss of consciousness is usually brief or does not occur. Such disabilities, however, are less difficult to assess, and the above figures serve to show the close relationship between the severity of general cerebral injury indicated by P. T. A. and residual damage in intellectual capacity.

Finally, the close similarity between the post-concussion syndrome in all its aspects and the so-called "effort syndrome" may be emphasized. Both might be defined as special forms of nervous reaction following at an interval either the possibility or the actuality of damage to the organ concerned.

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DISABLING CHANGES IN THE HANDS RESEMBLING SCLERODACTYLIA FOLLOWING MYOCARDIAL INFARCTION *

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Disabling trophic changes and deformities of the hands and fingers resulting from local ischemia are well recognized sequelae of "external" vasoconstriction from the splinting of injured hands and of "intrinsic" vasoconstriction from overactivity of the sympathetic nervous system. Scleroderma and sclerodactylia develop in Raynaud's disease and are regarded as among its most troublesome complications.[1] Similar trophic changes in the hands occurring as a sequel of acute myocardial infarction in 39 of 178 (21.8 per cent) consecutive cases of myocardial infarction are the subject of this report.

The first case (Case 18 in table 1), was referred early in 1937 by Dr. F. R. Schemm, an associate in the Great Falls Clinic, and was regarded as a case of "rheumatoid arthritis." When three similar cases were encountered that year on the cardiology service they were referred by him with the idea that a clinical syndrome might be being overlooked.

The appearance and course of these alterations were not similar to those seen in arthritis. The changes resembled very closely, however, those described as occurring in the hands of patients suffering with scleroderma and of patients having an abortive form of Raynaud's disease. In the literature,[2, 3] under the term sclerodactylia (hard fingers), is a description of a syndrome which is the prototype of the changes observed in the fingers of the four cases seen in 1937. No reference in the literature available in 1937 is made to any association between myocardial infarction and sclerodactylia, unless this sentence of Barker's [3] is significant: "I have found in most of my cases (of scleroderma) which develop late in life, organic disease of the heart and vascular system."

The Changes in the Hands

The first symptoms which attracted the attention of the patient and which appeared from three to 16 weeks after the acute myocardial infarction in this series were pain and stiffness of the fingers. Uniform, firm, bilateral, symmetrical swelling of the entire hands including the fingers appeared. The swelling did not pit on pressure. The skin became smooth and tight, and the normal wrinkles in the skin were more shallow or were entirely obliterated. This was true especially of the transverse wrinkles over the dorsum of the fingers. Color changes in the hands occurred, varying from

* Received for publication August 4, 1942.
From the Medical Department of the Great Falls Clinic, Great Falls, Montana.

TABLE I

Case No.	Age and Sex	Date of Infarction	EKG Findings	Anginal Syndrome	Radiation Anginal Pain	Interval Between Infarction and "Joint" Symptoms	"Joint" Affected First	Early Status					Previous Rheumatic History	Present Status				Remarks
								Distribution of Pain						Hands		Cntrtn Palmar Fascia	Stiff Shoulders	
								Shoulders		Hands		Other Joints		Atrophy	Limitn Motion			
								R	L	R	L							
1.	47 M	2-25-41	Diagnostic of infarction. Anterior	Present	L arm	6 weeks	"Hands"	0	+	+	+	0	0	++	++	++	0	Markedly limited by angina of effort and stiffness of hands. No foci.
2.	48 M	9-1-40	Diagnostic of infarction. Posterior	Present	L arm	12 weeks	R hand	0	+	+	+	R knee	0	+	+	0	0	Working as chef. Foci: Tonsils and teeth. (Has bronchial asthma.)
3.	58 F	10-31-40	Compatible with post. Infarction	Present	No radiation	6 weeks	R hand	+	+	+	+	0	0	++	++	++	0	Cardiac cripple. Cholecystostomy 1941. No other foci.
4.	63 F	4-27-39	Diagnostic of infarction. Anterior	Present	R shoulder	4 weeks	R shoulder	+	0	+	+	0	0	++++	++++	+++	0	Partially disabled by hands and heart. No foci.
5.	70 F	3-21-40	Diagnostic of infarction. Anterior and posterior	Present	No radiation	4 weeks	Hands	+	0	+	+	0	0	+++	++++	+	+	Disabled by hands and heart. Death 10-2-40, agranulocytosis. No foci.
6.	73 F	10-2-37	Old EKG shows myocardial disease. No EKG taken since infarction	Present	No radiation	10 weeks	R shoulder	+	+	+	+	Knees and elbows	Rh. Fever as child. Hypertr. arth. for 15 yrs.	++	++	++	+	No other foci. Cholecystectomy 8-11-37. Hypertrophic arthritis present.
7.	53 M	5-21-40	Diagnostic of infarction. Anterior	Present	L arm	9 weeks	Shoulders	0	+	+	+	0	0	+++	+++	+	0	Cardiac cripple. No foci. Moderate subluxation fingers.
8.	64 M	10-13-39	Diagnostic of infarction. Anterior	Present	R arm	8 weeks	R shoulder	+	0	+	+	R knee	0	+	+	+	+	Adenoma of prostate, mild cystitis. Sudden death Sept. 1940.
9.	68 M	6-15-37	Diagnostic of infarction. Anterior	Present	Both shoulders	8 weeks	R shoulder	+	+	+	+	0	0	+++	+++	++	+	Cardiac cripple—hands badly disabled. No foci.

TABLE I—*Continued*

Case No.	Age and Sex	Date of Infarction	EKG Findings	Anginal Syndrome	Radiation Anginal Pain	Interval Between Infarction and "Joint" Symptoms	"Joint" Affected First	Early Status					Previous Rheumatic History	Present Status				Remarks
								Distribution of Pain						Hands				
								Shoulders		Hands		Other Joints		Atrophy	Limitn Motion	Cntrtn Palmar Fascia	Stiff Shoulders	
								R	L	R	L							
10.	39 M	2–12–41	Compatible with recent infarction. Q_3 deep. S/T_1 depressed	Present	Both arms	6 weeks	Both shoulders	+	+	+	+	0	0	0	0	0	0	Activity restricted because of heart. No other disability. No foci.
11.	60 F	1–25–41	Diagnostic of infarction. Posterior	Present	Both arms	5 weeks	R shoulder	+	+	+	+	0	0	+	+	+	+	Activity markedly limited by angina of effort.
12.	55 F	1–3–38	Diagnostic of infarction. Atyp. post. Atyp. LBBB QRS .18 sec.	Present	L arm	3 weeks	R shoulder	0	+	+	+	0	0	++	+	0	++	Activity limited by angina of effort to light housework.
13.	51 M	6–26–40	Diagnostic of infarction. Posterior	Present	L arm and neck	6 weeks	L shoulder	0	+	+	+	0	0	+++	+++	+	0	Disabled by heart and hands. No foci.
14.	80 M	9–21–40 (several infarctions)	Diagnostic of infarction. Anterior LBBB QRS .18 sec.	Present	No radiation	Indefinite	Indefinite	0	0	+	+	Vague	0	+	++	0	+	Died 10–2–41—pulmonary embolism. No foci.
15.	54 F	Fall 1937	No definite abnormalities. LVP. QRS .10 sec.	Present	L arm and shoulder	12 weeks	L shoulder	0	+	+	+	0	0	+	+	+	+	Limited to light housework by heart and hands. No foci.
16.	51 F	5–11–39	Diagnostic of infarction. Posterior	Present	Both shoulders	8 weeks	R shoulder	+	0	+	+	0	Rh. fever age 6	++	++	++	0	Limited by angina of effort—stiffness right hand. No foci.
17.	56 M	4–2–41	Not taken	Present	L arm	12 weeks	L shoulder	0	+	+	+	0	0	++	++	0	0	Activity markedly restricted by angina of effort.
18.	60 M	12–4–36	Diagnostic of infarction. Anterior	Present	L arm	12 weeks	L shoulder	0	+	+	+	0	0	+++	+++	++	+	Completely disabled by angina of effort. Marked contraction deformity. No focus.

TABLE I—*Continued*

Case No.	Age and Sex	Date of Infarction	EKG Findings	Anginal Syndrome	Radiation Anginal Pain	Interval Between Infarction and "Joint" Symptoms	"Joint" Affected First	Early Status					Previous Rheumatic History	Present Status				Remarks
								Distribution of Pain						Hands		Cntrtn Palmar Fascia	Stiff Shoulders	
								Shoulders		Hands		Other Joints		Atrophy	Limitn Motion			
								R	L	R	L							
19.	61 M	1–9–41	Not diagnostic of; compatible with infarction. Low T_1; inverted T_3; notched T_4	Present	L shoulder	6 weeks	"Hands"	0	+	+	+	0	0	++	++	+	+	No foci. Activities much restricted by hands and anginal syndrome.
20.	60 M	3–16–38	Compatible with infarction, posterior. (Taken 6–3–38)	Present	Both arms	16 weeks	Both shoulders	+	+	+	+	0	0	+	+	0	0	Moderate restriction of activities because of angina of effort.
21.	66 M	(6–15–39) and *3–12–41*	Diagnostic of infarction. Anterior	Present	Both arms	4 weeks (after 3–12–41)	R shoulder	+	+	?	?	0	St. Vitus Dance age 12	?	?	?	+	No foci. Last seen 4–7–41. Died suddenly 5–29–41. See autopsy report.*
22.	68 F	Dec. 1938 Silent infarction	Diagnostic of infarction. Posterior. A–V dissociation. Aur. 70, ventr. 45	Present	Both shoulders	Approx. 5 weeks	L shoulder	+	+	+	+	0	0	++	+++	++	+	Activities limited because of angina of effort and stiffness of hands. No foci.
23.	57 M	1–2–38	Diagnostic of infarction. Ant. and post. QRS .16 sec. LBBB	Present	L arm	12 weeks	L shoulder	0	+	+	+	0	Rh. fever age 16	+	+	+	+	Activities limited because of angina of effort and stiff shoulders.
24.	62 M	4–10–41	Diagnostic of infarction. Location indeterminate	Present	Both arms	10 weeks	Both shoulders	+	+	+	+	0	0	+	+	0	0	Activity limited because of angina of effort.
25.	71 F	9–18–39	Compatible with infarction. (T_1 inverted)	Present	shoulders	12 weeks	Both shoulders	+	+	+	+	R knee	Hypertr. arthr. for 19 yrs.	+	++	++	+	Markedly limited because of angina of effort and stiffness of hands. No foci.

* Died in California; autopsy report through courtesy of Drs. J. E. Kohler and J. M. Askey: Rheumatic valvular disease with 20 per cent stenosis mitral valve and deformed aortic valve. Right coronary artery site of partially recanalized occlusion 1 cm. in length. Fresh red thrombus middle third of left descending branch of very sclerotic left coronary artery. Left shoulder joint removed in toto; no gross or microscopic pathological changes.

TABLE I—*Continued*

Case No.	Age and Sex	Date of Infarction	EKG Findings	Anginal Syndrome	Radiation Anginal Pain	Interval Between Infarction and "Joint" Symptoms	"Joint" Affected First	Early Status					Previous Rheumatic History	Present Status				Remarks
								Distribution of Pain						Hands				
								Shoulders		Hands		Other Joints		Atrophy	Limitn Motion	Cntrtn Palmar Fascia	Stiff Shoulders	
								R	L	R	L							
26.	73 F	6–9–41	EKG not taken	Present	L shoulder	8 weeks	Both shoulders	+	+	+	+	R knee	"Rheumatism" 1929 (Pain R knee)	0	+	+	+	Does own housework. Has mild hypertrophic arthritis. No foci.
27.	55 F	Fall 1939 (Multiple infarctions)	Compatible with infarction. QRS .16 sec. Auric. Fibr. T_1, T_2 low	Present	No radiation	Indefinite, established by Spring of 1940	L shoulder	0	+	+	+	0	0	+	+	0	+	Markedly limited by cardiac insufficiency. Angina mild. No foci.
28.	79 F	10–1–38	Diagnostic of infarction. Prob. ant. (3 leads only)	Present	Arms and shoulders	4 months	Shoulders	+	+	+	+	0	"Rheumatism" R foot age 60	+	+	0	+	Limited activity. No foci.
29.	46 M	10–5–40	Diagnostic of infarction. Anterior	Present	Arms and elbows	4 months	Shoulders	0	+	+	+	0	0	0	+	0	0	Moderate limitation of activities because of angina of effort.
30.	46 M	5–1–40	Not diagnostic of infarction. Compatible with myocardial disease	Present	Arms	3 months	Shoulders	+	+	+	+	0	0	+	+	+	+	No foci; no particular limitation of clerical activities.
31.	56 M	8–19–41	Diagnostic of infarction. Anterior. Atyp. LBBB QRS .16 sec. (Auric. Fib.)	Present	No radiation	8 weeks	Hands	0	0	+	+	0	0	0	+	0	0	No foci; activities restricted because of recent infarction.
32.	59 F	(Earliest) (6–6–34) *3–16–39* *6–20–39*	Diagnostic of infarction. Posterior *Anterior*	Present	Both arms	16 weeks	L shoulder	0	+	+	+	0	R knee	++	++	0	0	Intermittent claudication right calf 4–5–37; diabetes mellitus. Death 5–31–40.
33.	45 F	3–6–41	Diagnostic of infarction. Ant. and post.	Present	Both arms	16 weeks	Hands	0	0	+	+	0	Rh. fever age 6	+	++	0	0	Completely disabled by heart—increasing stiffness of hands. No foci.

TABLE I—*Continued*

Case No.	Age and Sex	Date of Infarction	EKG Findings	Anginal Syndrome	Radiation Anginal Pain	Interval Between Infarction and "Joint" Symptoms	"Joint" Affected First	Early Status					Previous Rheumatic History	Present Status				Remarks
								Distribution of Pain						Hands				
								Shoulders		Hands		Other Joints		Atrophy	Limitn Motion	Cntrtn Palmar Fascia	Stiff Shoulders	
								R	L	R	L							
34.	64 M	6–26–41	Diagnostic of infarction. Anterior	Present	Right arm	12 weeks	R shoulder	+	+	+	+	0	0	+	+	0	+	Limited by cardiac insufficiency.
35.	47 M	7–16–41	Diagnostic of infarction, location indeterminate	Present	None	3 weeks	Hands	+	+	+	+	0	0	+	++	0	0	Limited by cardiac insufficiency. Has cardiovascular syphilis.
36.	70 F	9–21–41	Diagnostic of infarction. Posterior	Present	Both arms	6 weeks	Hands	+	+	+	+	0	Hypertrophic arthritis of R hand	++	+++	+	+	Limited activity.
37.	72 F	8–6–41	Diagnostic of infarction. Posterior. Auricular fibrillation	Present	None	5 weeks	Hands	0	0	+	+	0	0	+	+	+	0	Died suddenly 6–2–42.
38.	74 M	12–30–41	Diagnostic of infarction. Anterior	Present	R arm	8 weeks	R shoulder	+	+	+	+	0	0	+	+	+	+	Moderate limitation of physical activities.
39.	46 M	3–1–42	Diagnostic of infarction. Anterior. Right ventricular preponderance	Present	None	8 weeks	Hands	0	0	+	+	0	0	+	++	0	0	Marked limitation of physical activities because of status asthmaticus and cor pulmonale.

an erythema to different grades of cyanosis. The hands and fingers were cold to the touch, and no consistent moistness, dryness, or sensory changes were noted. No striking changes were present in the volume of the pulse in the radial or brachial arteries, although, for the most part, these vessels showed varying degrees of thickening and sclerosis. The fingers could never be fully extended or flexed, and when they were manipulated pain accompanied the increased motion. Effusion in the joints and crepitation never developed. No nodules or nodes were observed except in those patients who had a preëxisting hypertrophic arthritis. These characteristics were noted in the early stages of all the cases and varied only in degree.

With the passage of time and regardless of therapy, the swelling of the fingers and hands subsided, but no particular changes occurred in the pain or stiffness of the fingers. The skin which first appeared thin and glossy now became thickened and dull in color, sometimes bronzed. The joints and bony prominences of the hands and fingers were more apparent because of shrinkage of the soft tissues over the phalangeal shafts. Movements of the fingers were limited and painful, and neither complete flexion nor extension could be accomplished. The soft tissues overlying the phalanges on the dorsal surfaces appeared to become more tightly attached to the underlying structures. Soft tissue atrophy made the metacarpals stand out and the tendons become more prominent. The contracture of the palmar fascia was not as apparent at this stage as later in the course of the disease. In some longstanding cases the roentgenograms showed disuse atrophy of the bone. These characteristics of the hands and fingers were constant in the later stages in all cases although variable in degree in individual patients.

The functional capacity of the fingers was quite variable. Some patients developed severe contractures of the fingers, whereas others had few residual deformities and little impairment of motion, though function earlier may have been greatly impaired. In the more severe cases the hands of these patients felt stiff, withered and wooden, and when grasped one felt that all softness, pliability and flexibility had been lost, justifying the descriptive term sclerodactylia or "hard fingers." The changes never progressed further and in many the function, appearance, and texture of the hand approached the normal. Areas of gangrene and the formation of ulcers were never observed. No pain or impaired function of the elbows or wrists ever occurred. No other joints of the body, except the shoulders, changed in function or gross appearance. No change occurred in any preëxisting arthritis or disability in other joints.

The syndrome described above most closely resembled descriptions of the changes recorded as occurring in the hands and fingers found in the sclerodactylia of scleroderma and Raynaud's disease.[1, 2, 3]

Clinical Material and Observations

The 39 patients in this series seen in the past five years were encountered in the cardiology service and were referred to the arthritis service where they

were followed and treated because of the painful disability of the hands following their myocardial infarctions. They came from a group of approximately 178 cases of myocardial infarction in a series of approximately 375 consecutive cases of grossly evident heart disease. In this series of 375 cases *of all forms* of severe heart disease no painful disability of the hands of this nature developed unless a myocardial infarction had occurred.

Diagnosis of myocardial infarction was made on the basis of a typical clinical syndrome in all patients and electrocardiographic studies which were compatible with, or diagnostic of, myocardial infarction in all but five patients. Electrocardiographic studies did not support the clinical diagnosis in two patients, and no electrocardiograms were made in three patients. In these five patients the clinical diagnosis of myocardial infarction was supported by the presence of leukocytosis and fever and the development of such phenomena as a severe anginal syndrome, a pericardial friction rub, myocardial failure, emboli, etc.

Table 1 summarizes the clinical observations on the 39 cases. Four of these cases are presented in greater detail, with pertinent photographs, roentgenograms and electrocardiograms.

Summary of Data From Table 1

1. *Age and Sex:* The average age in years of the 39 patients in this series was 58.3. Twenty-three patients were male and 16 were female.

2. *Electrocardiographic Findings:* Electrocardiographic studies were compatible with, or "diagnostic" of, myocardial infarction in all but five patients. Three of these patients had no electrocardiograms and the electrocardiographic study did not support the clinical syndrome in the other two.

3. *Anginal Syndrome:* This symptom complex occurred in all of the 39 cases. Its importance in the development of the changes in the hands is discussed later.

4. *Radiation of Anginal Pain:* The site of radiation of the anginal pain did have some definite relationship to the development of *shoulder pains* and stiffness. The hand changes were bilateral and constant and there was no correlation between the site of radiation of the anginal pain and the development of the *hand changes.*

5. *Interval Between Infarction and "Joint Symptoms":* Minimum time interval was three weeks, maximum time interval 16 weeks. The time interval seemed to have no relation to the severity of the changes in the hands.

6. *"Joint" First Affected:*

	Cases		Cases
Both shoulders	9	Both hands	9
Left shoulder	8	Left hand	0
Right shoulder	10	Right hand	2
		Not known	1

The shoulder was the first "joint" involved in 27 patients. Such a high incidence of initial shoulder pain has been noted by others and has been attributed to a "periarthritis."

7. *The Distribution of Pain (early status):* Pain occurred in both hands in 38 of the 39 cases. (Case 21 was observed only during the first two weeks of the nine weeks before sudden death.) Thirty-four patients had pain in one or both shoulders; five had pains in "other joints." Four of these had hypertrophic arthritis changes in the "other joints" involved.

The data show the frequency of the pain in the hands in this syndrome, pain being definitely present in all but one, in whom its absence was not determined.

The relation of the radiation of anginal pain to the appearance of early shoulder pain follows:

Radiation of Anginal Pain		Early Shoulder Pain	
To both upper extremities	15	Both shoulders	11
		Left shoulder only	2
		Right shoulder only	1
		No shoulder pain	1
To left upper extremity only	11	Left shoulder only	10
		Both shoulders	1
To right upper extremity only	4	Both shoulders	2
		Right shoulder only	2
No radiation to upper extremities	9	No shoulder pain	4
		Both shoulders	3
		Right shoulder	1
		Left shoulder	1

See discussion of the probable relationship of the radiation of anginal pain to shoulder pain and disability under heading of "periarthritis."

8. *Previous Rheumatic History:* Ten patients had a previous rheumatic history, four of whom had rheumatic fever in childhood. Four patients had hypertrophic arthritis, two had "rheumatism" of the right knee, one had rheumatism of the right foot and one had had "St. Vitus Dance." One patient had had both hypertrophic arthritis and rheumatic fever. No history could be obtained in any of our cases of "preëxisting arthritis" in the shoulders. In this series no change in preëxisting joint symptoms or deformities occurred as a result of the infarctions.

9. *Present Status (when last seen):*

Atrophy of Hands: All but four patients showed atrophy of a discernible degree. Eighteen showed one plus atrophy, 10 had two plus atrophy, five had three plus and one four plus atrophy, and in one patient the degree of atrophy was not determined. Atrophy is a predominant feature in the later stages of the syndrome.

Limitation of Motion in Hands: All but two patients had limitation of

motion of the fingers of varying degrees; one patient had no limitation of motion; 17 patients had one plus; 12 had two plus; six had three plus; two had four plus and in one the degree of limitation was not determined. Limitation of motion is a predominant feature in the later stages of the syndrome.

Contracture of Palmar Fascia: Sixteen patients had no contracture, 13 had one plus contracture, eight had two plus contracture, one had three plus contracture.

Stiffness of Shoulders: Seventeen patients had no residual stiffness of the shoulders; 22 patients had residual stiffness of the shoulders.

Case Reports

Case 4. M. J. C., female, aged 63, housewife. There was nothing relevant in the past history or in the family history except that one sister had atrophic arthritis.

Present Illness: On April 27, 1939 the patient had a severe attack, characterized by precordial pain which radiated to the right shoulder and lasted for fifty minutes, and was accompanied by orthopnea, nausea and vomiting, and shock. She was admitted

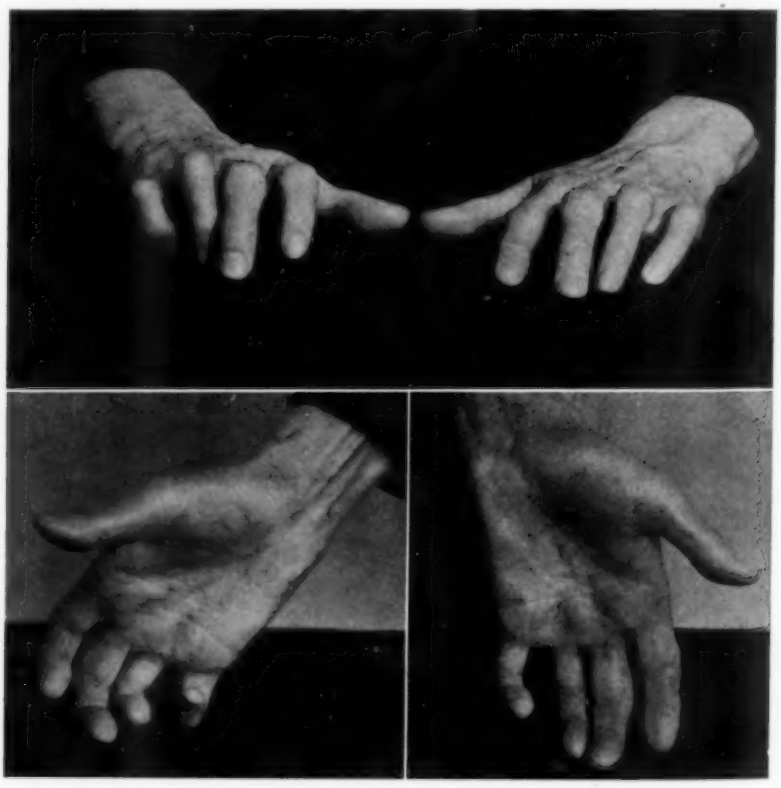

Fig. 1. *Case 4:* Illustrating the claw-like appearance of the hands in a late stage. Dorsal view shows prominence of joints due to atrophy of soft tissues of phalanges and the tight stretching of the skin over the underlying structures. Skin appears glossy and transverse wrinkles have disappeared. Palmar view shows absence of ulnar deviation of the wrist; a contraction of palmar fascia and the maximum possible extension of the fingers.

to the hospital on the third day. Pulse rate was 100 to 120, weak and irregular. There was Cheyne-Stokes' respiration. Blood pressure was 70 mm, Hg systolic and 50 mm. diastolic. A pericardial friction rub was present. There was moderate pitting edema of the ankles, and there were râles at both lung bases. The extremities showed no evidence of muscle, nerve, bone or joint disease. Urine showed two plus albumin;

FIG. 2. *Case 7:* Lateral view shows maximum possible flexion of the fingers. Dorsal view shows subluxations resulting from violent efforts to achieve full extension of the fingers; no effusion or fusiform swelling of the joints and no ulnar deviation of the wrist. Skin appears tightly applied to the phalanges and atrophic and bronzed over the dorsum of the hand.

leukocytes 15,400, 74 per cent polymorphonuclears. Electrocardiogram is shown in figure 7. A critical period of oliguria, vomiting and shock lasted 10 days. She was discharged from the hospital on May 25, to continue her convalescence at home.

One week later she complained of pain and stiffness in the right shoulder, but the left shoulder and both elbows and wrists were asymptomatic. Three weeks later the hands began to feel numb and unwieldy and difficulty in movement of the fingers developed. The hands were held semiflexed. There was a uniform swelling without pitting edema extending to the finger tips. The skin appeared glossy and erythematous; and normal markings, particularly the transverse wrinkles over the dorsal phalangeal joints, were indistinct. The right shoulder was unchanged from the previous examination and function was normal in the left shoulder and both elbows and wrists.

Her cardiac status remained precarious; another myocardial infarction occurred on August 22, 1939, and anginal attacks occurred in spite of restricted activity. Pain and stiffness of the right shoulder persisted and the hands became gradually worse. She made no real effort to maintain motion as did the others whose eventual crippling was less (cases 7, 9, 19), and with time the flexion deformity in the fingers became fixed and permanent (figure 5). The palmar fascia was markedly contracted. Stiffness and disability of the fingers became her chief complaint, although mild angina persisted.

Examination on April 21, 1941 revealed entirely normal function of the left shoulder. The right arm could be raised above the head but not as far as the left, and

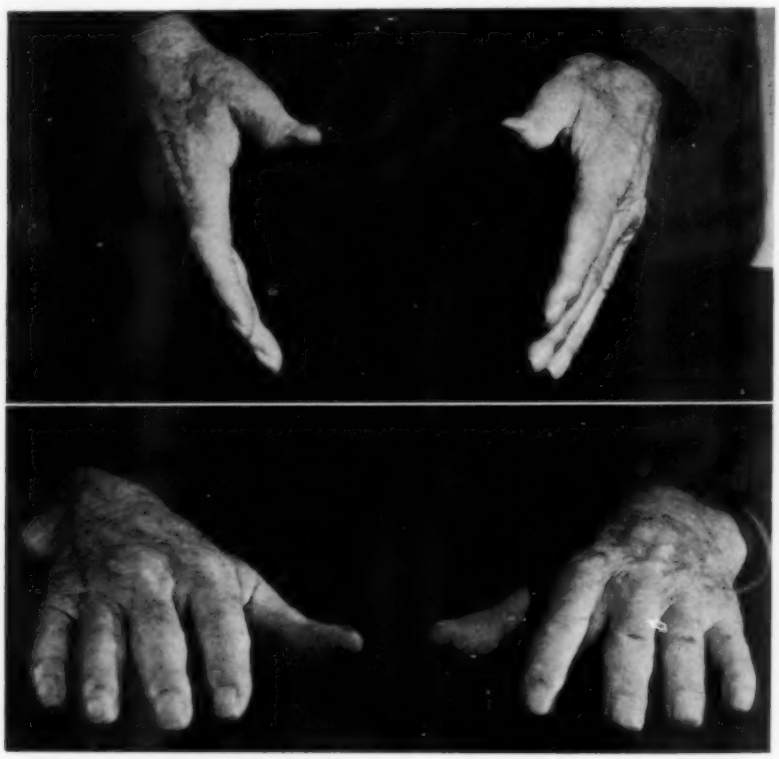

FIG. 3. *Case 9:* Lateral view shows maximum attainable extension in a late stage after much physiotherapy in an elderly patient. Dorsal view shows the glossy tightly applied skin over the fingers, and the false appearance of enlargement of the inter-phalangeal joints due to atrophy of the soft tissue of the phalanges.

abduction and rotation were not far from normal. The elbows and wrists were entirely asymptomatic and their function normal, as they had been throughout the entire course of her illness. The hands showed symmetrical anatomical and functional changes. Neither full flexion nor extension of the fingers was possible. The hands appeared claw-like and nearly immobile. Flexion deformity was most marked in the little and ring fingers. The skin no longer showed the uniform erythema; it felt thickened, seemed to be attached to the subcutaneous tissue and stretched over the bones. The palmar fascia was markedly contracted. Neither subcutaneous nodules nor Heberden's nodes were present. The joints, especially the distal joints,

were more or less fixed, but no crepitation or effusion was present (figure 5). The joints stood out because of atrophy of the soft tissues of the phalanges. The appearance of the hands was the same in May 1942 (figure 1).

This case illustrates the extreme deformities possible after myocardial infarction. The patient had had no "rheumatism" previous to this incident.

Case 7. L. B. G., male, aged 48, a rancher, had had known cardiac enlargement and mild hypertension since 1935. He was seen at his ranch home on May 22, 1940,

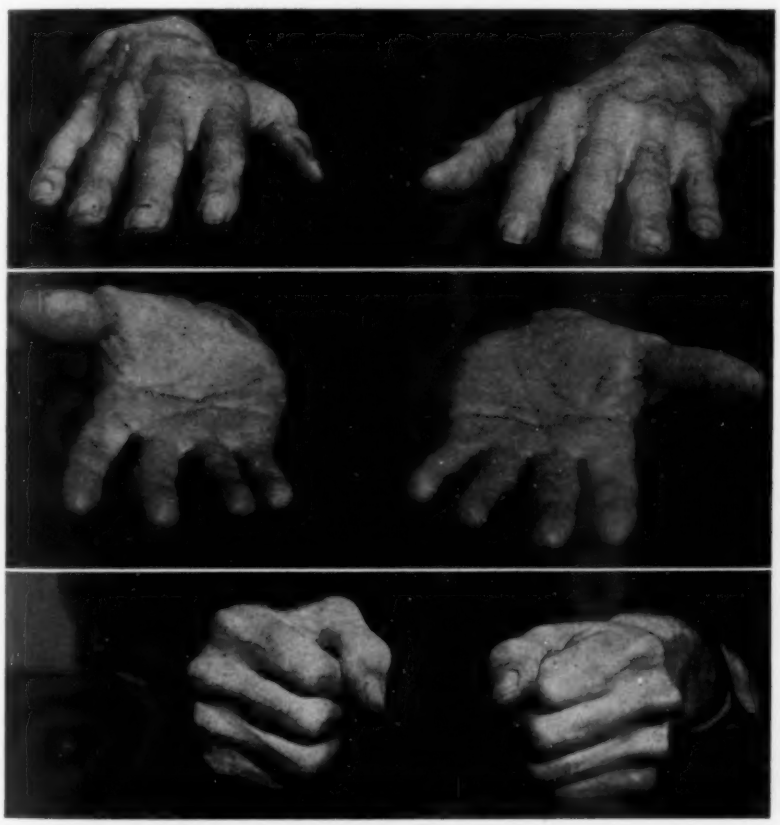

FIG. 4. *Case 13:* Dorsal view shows atrophy of soft tissues of phalanges and dorsum of hand, and prominence of phalangeal joints due to soft tissue shrinkage. Palmar view shows maximum extension of the fingers and moderate palmar fascia contraction. Fist-view indicates maximum possible flexion. Note that the middle row of phalanges makes an obtuse angle with the proximal row.

in a state of collapse, complaining of severe crushing pain in the precordium, with radiation to the left arm. He was admitted to hospital in a critical state, with pulse rate of 64, heart tones of extremely poor quality, and blood pressure of 140 mm. Hg systolic and 90 mm. diastolic. Leukocytes numbered 18,000, with 93 per cent polymorphonuclears, and temperature was 103° F. on the third day. On June 4, a paroxysmal ventricular tachycardia developed (serial electrocardiogram, figure 7). Following recovery from this episode there was gradual improvement. He was dismissed on June 28, to continue convalescence at home; there were no joint symptoms at this time.

Five weeks later he developed stiffness and pain in the shoulders, especially the left, and in both hands. Examination on August 27, 1940 showed limitation of motion, particularly in abduction, in both shoulders, more marked in the left than the right. There was no pain or limitation of motion in the elbows or wrists. The hands, especially the fingers, were uniformly swollen. The skin appeared tense and erythematous, but no pitting edema was present. The fingers were held slightly flexed and movement was greatly limited in all the phalangeal joints. Pain was severe with passive motion. No effusion or crepitation was present. No subluxation of the phalangeal joints was present.

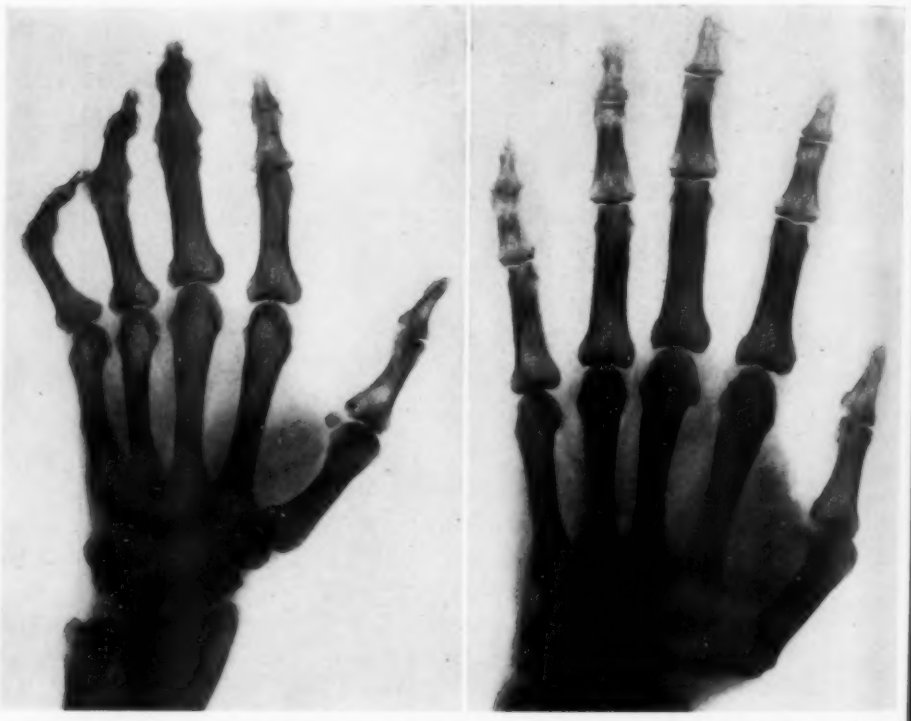

FIG. 5. *Case 4:* (*Left*) Claw-like fixation of the fingers renders it difficult to demonstrate that the inter-phalangeal surfaces are smooth and that there is no obliteration of the joint spaces. No proliferation of bone. Atrophy of bone is apparent.
Case 7: (*Right*) Marked decalcification. No proliferation, no increase or obliteration of joint space or other changes commonly seen in arthritis despite the fact that subluxations of the distal phalanges were present.

Two months later the condition and appearance of the hands had changed; the skin had lost its erythematous color, was less glossy, and felt thickened and seemed attached to the underlying structure. The patient had made strenuous efforts to regain full extension of his fingers, and a beginning subluxation of several of the distal phalanges had developed. A mild Dupuytren's contracture was present. There was no ulnar deviation of the hand. There were no subcutaneous nodes or nodules, and no joint crepitation or effusion. The fingers could be fully extended where subluxation had occurred, but flexion was incomplete (figures 2 and 5).

The severity of this man's infarction and the degree of change in the hands were about in the same proportion. He was the only patient who made violent efforts to

overcome his limitation of motion and who developed any subluxations of the phalanges.

Case 9. J. A. M., male, aged 68, clergyman. There was nothing relevant in family or past histories.

Present Illness. On June 15, 1937 an attack of severe precordial pain lasted two hours, radiating to both shoulders. On admission the patient was apprehensive. There was marked dyspnea; pulse was 90, regular; there was a blowing systolic apical murmur transmitted to the axilla; blood pressure was 170 mm. Hg systolic and 110 mm. diastolic. The extremities showed no evidence of muscle, nerve or bone

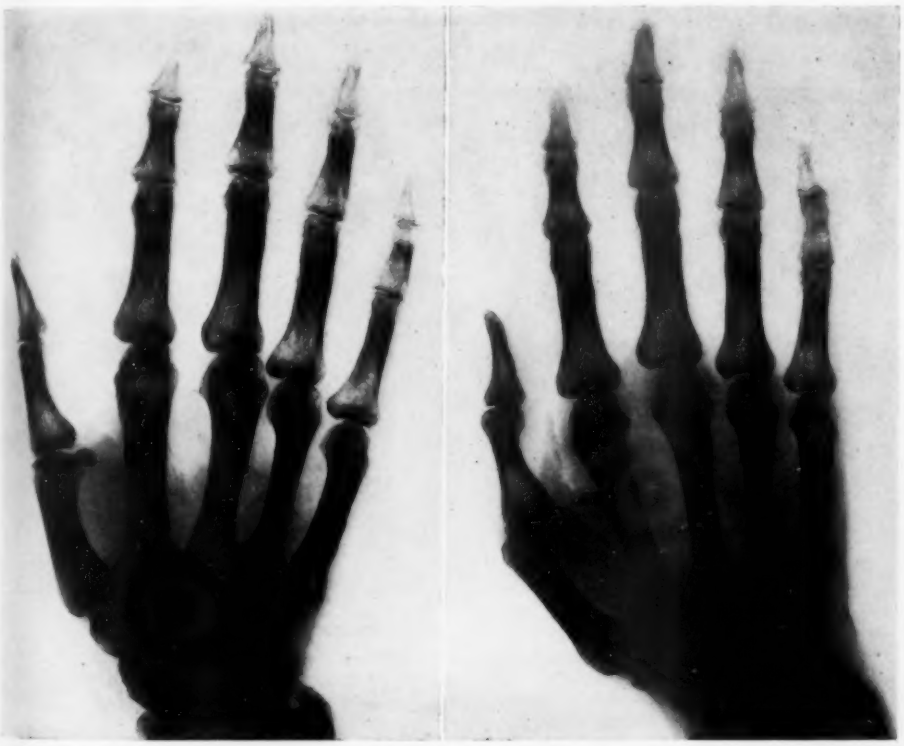

FIG. 6. *Case 9:* (*Left*) Very little joint space change for an elderly patient. Marked arteriosclerosis of the vessels of the hands as indicated by calcium shadow between second and third metacarpals.

Case 13: (*Right*) Decalcification of the phalanges, no changes in the wrist and very little change in the articulating surfaces of the phalanges.

or joint disease. There was no oral or dental sepsis, nor were there any signs of prostatic infection. Recovery was slow. Electrocardiogram is shown in figure 7.

Eight weeks after the attack stiffness of the right shoulder joint was followed by pain and stiffness in the left shoulder and in both hands. The shoulders showed limitation of motion. Elbows and wrists were normal and asymptomatic. The hands, and especially the fingers, showed swelling without pitting and a reddish cyanosis. The skin appeared tense, and the normal wrinkles of the hands and fingers were almost obliterated, both on the palmar and dorsal surfaces. The fingers were more comfortable semiflexed and painful if manipulated. There were no tender nodes or nodules, and no joint effusion or crepitation.

Four months later the erythematous swelling of the skin of the hands had disappeared, and the fingers were stiffened and felt wooden. The skin was thickened and gave the impression of being shrunken over the bones and somewhat fixed to the subcutaneous tissue; the interossei muscles showed atrophy; the phalangeal joints appeared enlarged as a result of the atrophy of the soft tissues of the phalanges. There was no crepitation or effusion in the joints (figure 6). Neither full flexion nor full extension could be accomplished, flexion being more limited than extension (figure 3).

This case showed early extreme vasomotor changes in the hands. Marked arteriosclerosis of the vessels of the hands may have been a factor in the persistence

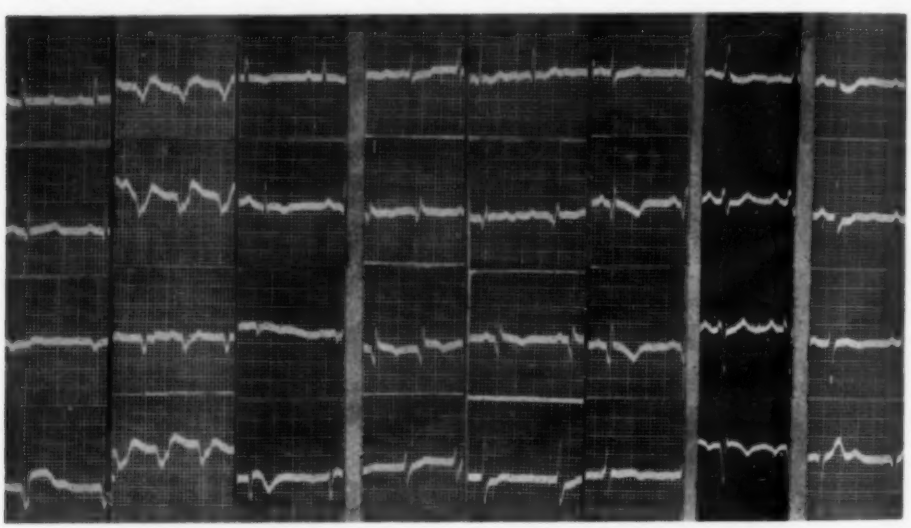

Fig. 7. Tracings from the four cases reported in detail.*

Case 7, 5/22/40. Changes compatible with acute myocardial infarction; anterior location; no digitalis. *6/10/40.* Paroxysmal ventricular tachycardia (on longer tracing ventricular rate is found to be more rapid than auricular rate, ratio 5:3). *6/12/40.* Further changes compatible with recent acute infarction, anterior location.

Case 13, 6/26/40. Compatible with acute infarction; no digitalis. *6/27/40.* Transient fibrillation and flutter occurring while tracing was being made. *7/5/40.* Further changes diagnostic of acute myocardial infarction, posterior location; no digitalis.

Case 4, 4/29/39. Compatible with recent anterior infarction.

Case 9, 6/20/37. Compatible with myocardial infarction, anterior location.

* Chest lead is Standard American Heart Association IV F.

of the changes (figure 6). Two years after the attack the hands were about the same. Restriction in flexion was marked, and when his hand was grasped it felt stiff and wooden.

Case 13. C. B., male, merchant. There was nothing relevant in his uneventful past history. A mild angina became gradually worse until June 26, 1940. He was admitted to the hospital on account of agonizing pain in the left chest which radiated to the left arm and the left side of the neck and was unrelieved by nitrites. There was marked dyspnea and fear of impending death. Leukocytes reached 20,000 with 84 per cent polymorphonuclears in 48 hours. Heart sounds were enfeebled. There was moderate enlargement, with no murmurs or irregularity. Blood pressure was 132

mm. Hg systolic and 100 mm. diastolic. There was no evidence of muscle, nerve, bone or joint disease. Tonsils were normal appearing and atrophic. There was no oral sepsis.

The patient's condition remained precarious for many weeks, with many attacks of angina decubitus. Transient auricular fibrillation developed on several occasions throughout his long hospitalization (serial electrocardiogram, figure 7).

No symptoms were noted in the joints until July 27, 1940, when he complained of stiffness and pain in his left shoulder. Three weeks later he noticed stiffness and pains in the fingers. Examination showed a uniform swelling of the hands and fingers without pitting. The skin showed a reddish cyanosis, and the normal wrinkles had disappeared. The fingers were held semiflexed and any movement, either passive or active, was associated with pain. His hands remained unchanged for many weeks, subjectively and objectively. At no time during his long hospitalization did he have pains in the elbows or wrists. By October 1940 the hands had changed considerably. The skin, which previously had been erythematous, now showed brownish pigment. Some of the glossiness and the "ironed out" appearance had disappeared. Difficulty was experienced in lifting the skin from the subcutaneous tissues. The interjoint spaces were shrunken, and the tendons appeared prominently on the dorsal and palmar surfaces. Movement of the fingers was greatly limited so that he was unable to move them much from a semiflexed position. There were no Heberden's nodes or nodules, and no fluid or crepitation in the finger joints. A definite palmar fascia contracture was apparent.

Following discharge he remained crippled by angina occurring with mild physical effort or emotional upsets. Examination on October 7, 1941 revealed right shoulder normal, left shoulder slightly limited in motion, particularly in abduction. The hands and fingers showed no improvement in function or change in appearance (figures 4 and 6).

This man had many mild anginal attacks following the severe, near lethal, myocardial infarction, and fear was a prominent feature of all the attacks. He stated after the more severe anginal attacks "my hands feel worse." His deformities were severe, particularly the atrophy and limitation of motion and although his degree of arteriosclerosis did not approach that of case 9, the deformities and functional disturbance were about the same. He illustrates the rôle of repeated attacks of pain associated with fear in the development of the syndrome.

Discussion

The incidence of disabling changes in the hands following myocardial infarction in this series is high, 39 patients or 21.8 per cent in 178 consecutive cases of myocardial infarction. We believe that it would be found to be as high or higher in any comparable series, were it not for certain factors: Some patients do not survive the initial infarction long enough to develop the syndrome (time in this series, three to 16 weeks); mild symptoms in the hands are so overshadowed by cardiac symptoms as not to be mentioned by the patient; the classifying of many cases of the type reported here as "rheumatoid" or "atrophic arthritis," and inability to obtain follow-up data on some cases.

Because of the frequency with which this syndrome follows myocardial infarction, its recognition may be important in substantiating the occurrence of a myocardial infarction in those patients in whom the electrocardiographic changes or clinical symptoms were not conclusive.

Differential Diagnosis

Rheumatoid Arthritis: The disabling changes in the hands following myocardial infarction are frequently mistaken for rheumatoid arthritis. Sharp contrasts in the clinical manifestations, however, make it obvious that this syndrome is not rheumatoid arthritis, but a distinct clinical entity which has the etiological, clinical, and morphologial criteria of sclerodactylia. It is probable that there are some etiological factors which are common to sclerodactylia and to some cases of rheumatoid arthritis. In both conditions the pathological changes are referred but not limited to the joints, that is, muscle, bone and fascia participate in the changes in the extremity. Joint involvement in rheumatoid arthritis may be strikingly symmetrical and bilateral, even though it is rarely limited to the hands, as is invariably the case in this syndrome. Studies of the nail beds which have been made in rheumatoid arthritis show fewer capillaries and capillaries of narrower caliber, not unlike the picture seen in sclerodactylia, and actually sympathectomy has been tried for symptomatic relief in both.

The most striking characteristic of this syndrome is uniformity. The mode of onset, clinical course, and the clinical manifestations follow a quite regular and uniform pattern. The changes which are limited to the hands are symmetrical and bilateral, and of approximately equal severity in the same individual.

In this syndrome the earliest changes occur in the skin of both hands. The skin appears edematous and glossy, and a feeling of tension and stiffness of the entire hand is complained of. In rheumatoid arthritis the skin does not show such consistent or uniform changes; tension occurs over one or more swollen joints. Instead of uniform discoloration of the skin which varies from pale violet to red, and is characteristic of this syndrome, in rheumatoid arthritis localized redness may occur only over the swollen joint itself. In this syndrome, the skin temperature is the same over the whole hand and not elevated, whereas in rheumatoid arthritis the temperature is often increased locally over an affected joint. The isolated fusiform swelling of the joint so typical in rheumatoid arthritis may exhibit extreme tenderness on lateral pressure, whereas the uniformly swollen fingers in this syndrome exhibit diffuse tenderness which is not especially localized to the joint. Although rheumatoid arthritis may involve several joints of the fingers simultaneously, the acuteness of the symptoms may be subsiding or stationary in one joint, at the same time that they are increasing in severity in an adjacent joint; by contrast in this syndrome, the acuteness of the symptoms is of more or less equal severity, bilaterally, and the progression or recession of symptoms is usually even and uniform in all the fingers. The stiffness in this syndrome involves the whole hand, and is not, as is often the case in rheumatoid arthritis, localized to a joint. Finally, in striking contrast to this syndrome, in rheumatoid arthritis, other joints such as the wrists, elbows and knees may be affected simultaneously with the hands. It is especially

in the early stage of this syndrome that the differential diagnosis presents difficulties, and then only if the rheumatoid arthritis is limited to both hands, which is uncommon.

Later, sharp deviations in the clinical course of the two conditions occur. In the syndrome the uniform swelling and discoloration of the skin gradually subside, the skin of the entire hand loses its elasticity and appears hard and leathery and uniformly attached to the underlying structures, stiffness rather than pain becomes more prominent, and the entire hand is held rigidly with the fingers semiflexed. In rheumatoid arthritis the skin appears parchment-like and tense over an isolated swollen joint in which effusion has occurred, so as to give the characteristic spindle-shaped finger; adjacent phalangeal joints of the same finger may appear normal and function well. Subluxations, so common in rheumatoid arthritis, occur rarely in this syndrome and only as a result of violent attempts to achieve extension of the fingers. Ulnar deviation and subcutaneous nodules so characteristic of rheumatoid arthritis do not occur. Contractions of the palmar aponeurosis of various degrees are common in the syndrome and unusual in rheumatoid arthritis.

Finally, the syndrome occurs usually after middle life in patients with severe cardiovascular disease and has a tendency to recession, in contrast to rheumatoid arthritis which begins usually before middle life in patients without cardiovascular disease, and has a strong tendency to progression and extension.

"Periarthritis": In the literature this term refers especially to the stiffness and pain in the shoulder which often follow myocardial infarction, and appeared in 74 per cent of 29 out of 39 patients in this series. We believe that the pain and stiffness in the shoulders and the syndrome of disabling changes in the hands are not related to one another even though they both follow myocardial infarction (paragraphs 6 and 7 under "Summary of data in table 1").

In this series of cases a preëxisting arthritis appeared to play no rôle, for none of the patients had symptoms referable to the shoulder joints previous to the infarction. The autopsy on case 21 (table 1) supports this view, as no gross or microscopic changes suggestive of an arthritis were found in the shoulder joint. Another point against the importance of "preëxisting arthritis," or "periarthritis," is the fact that elbows and wrists in this series showed no limitation of motion or pain.

It is not necessary to assume a "preëxisting arthritis" to account for the early shoulder pains and stiffness in the shoulders. The changes could be the result of an unconscious protective mechanism in which the patient holds the arm rigidly against the side of the chest to prevent recurrence of anginal pain. The fixed attitude of patients during an anginal attack is well known.

The important feature of the shoulder disability is the appearance of exquisitely tender areas about the shoulder joint and spine. Following myo-

cardial infarction tender areas may be noted in the skin, muscles, or other structures. The referred pain and tenderness were studied by MacKenzie, who felt that the stream of pain impulses from the heart in myocardial infarction altered the condition of the spinal gray matter ("irritable focus") so that impulses were sent to the corresponding segments of skin, body wall, etc., which accounted for tender areas in the skin (cutaneous hyperalgesia), tenderness in the muscles such as the trapezius and deltoid (muscular hyperalgesia) and tenderness over the first to fourth thoracic spines in diseases of the heart. Besides these sensory phenomena, motor effects such as painful contractions of corresponding groups of muscles like those of the shoulder girdle or intercostal muscles may also be produced[15] as a reflex response to the cardiac pain.

Suggestive support of this explanation of shoulder pain and stiffness may be found in the figures in paragraph 7 of the "Summary of data in table 1."

In conclusion, it is felt that the pain, stiffness, and limitation motion in the shoulder region develop because of voluntary or involuntary splinting of the joint on account of the fear of initiating recurrence of the anginal pain and because the shoulder itself is the site of reflex tenderness. The pain and the "tender points" are a peripheral reflex response to the anginal pain comparable to the pain and the tender point below the right scapula so often noted in gall-bladder disease. The shoulder symptoms are not considered to be related to the hand changes or to share in the chief etiologic factor of the hand changes, viz., ischemia produced chiefly by vasoconstriction of the arteries of the hands.

Theoretical Considerations

Certain anatomical and physiological considerations[15] make it appear reasonable to explain the disabling changes in the hands following myocardial infarction as due to nutritional disturbances (chiefly anoxia) resulting from local ischemia (vasoconstriction) and anoxemia in the hands and fingers. It does not appear necessary to assume the presence of a "preëxisting arthritis" or a gouty diathesis as other writers[9, 10, 11] have done.

These changes in the hands and fingers have been compared with the sclerodactylia of Raynaud's disease because of certain similarities in etiology, appearance and clinical course. The condition does not progress to the extremes of gangrene and trophic ulcers of the fingers as it does in some cases of Raynaud's disease, because one important mechanism, the vasoconstriction resulting from the cardiac pain, is relatively temporary and intermittent.

The limitation of the syndrome to the hands, to the exclusion of the elbows and wrists and other "joints" of the body (except for the shoulders which have been dealt with earlier), places the etiology on an anatomical basis, in which a local ischemia resulting from impaired function of the peripheral arteries of the hands is the localizing factor.

It is felt that the factors which are etiologic in the production of the local changes in the hands and fingers are:

1. Vasoconstriction of the peripheral arteries of the hands resulting from the cardiac pain.
2. Preëxisting arteriosclerotic narrowing of the vessels of the hands.
3. Anoxemia of varying duration and intensity resulting from the myocardial infarction.

Discussion of these three factors, all of which contribute to a state of anoxia of the tissues of the fingers, follows:

1. The Effects of the Vasoconstriction Caused by Pain: These are of the greatest importance in the development of the disabling changes in the hands following myocardial infarction. The pain here is regarded as occurring with either "spasm" or closure of coronary vessels. The changes in the hands do not develop where simple anginal attacks have not been interspersed with or followed by cardiac infarction. The infarction would appear to have a two-fold effect in producing changes in the hands. The greater effect is due to (a) reflex vasoconstriction of the peripheral arteries produced by the pain of the coronary closure which far exceeds the pain of simple anginal attacks in duration and intensity, and (b) vasoconstriction produced by the release of adrenalin as a result of fear or pain.

The nerve paths between the heart and hand have long been studied.[15] The pain impulses originate in the heart and pass by the sensory nerve fibers chiefly to the eighth cervical and the upper four thoracic nerve roots of the spinal cord. From here the pain is most often referred down the inside of the arms (Thoracic 1), and to the sides of the chest (Thoracic 1, 2, 3).[15] Rami from these segments of the cord connect with the lower cervical and upper thoracic sympathetic ganglia which furnished vasoconstrictor fibers to the upper extremity.

In connection with the distal vasoconstrictor effects of cardiac pain, it is important to recall that both the phenomena of Raynaud's disease and severe anginal pain may be relieved by cervicothoracic ganglionectomies. The importance of the nervous pathway between the heart and the hands is further emphasized by the demonstration that ice cubes held in the hands will lower "exertion tolerance" in cases with angina pectoris.[13]

It has been shown that the failure of cervicothoracic ganglionectomy in Raynaud's disease can be explained by the fact that there can be secreted a sufficient amount of adrenalin in response to emotions resulting from pain and fear to produce peripheral vasoconstriction. This indicates the importance of emotions, such as fear, in producing vasoconstriction of the peripheral arteries and *fear* is a prominent feature in the pain of coronary closure.

Hence, the anginal or occlusion pain may produce vasoconstriction of

the peripheral arteries directly through the cord (reflex arc) or indirectly through the higher centers (adrenal stimulation).

2. The Effects of Preëxisting Arteriosclerotic Narrowing of the Arteries of the Hands: Since occlusive vascular disorders are far more common in the lower extremities in general arteriosclerosis, it is evident that the presence of arteriosclerosis is of minor importance in the development of these changes in the hands; it merely makes a small, but perhaps often determining addition to the sum total of ischemia and nutritional deficiency. The chief determining factor remains the pain and its sequel of vasoconstriction.

3. The Effects of Anoxemia of Varying Duration and Intensity Resulting from the Myocardial Infarction: For the reasons outlined above it is believed that by far the most important effect of the myocardial infarction in the development of the changes in the hands is the increased vasoconstriction from pain and fear. However, it seems probable that during the acute phase of the infarction the lowered oxygen content of the blood, and possibly actual toxic substances liberated by the death of the cardiac muscle, add to the sum total of the nutritional deficiency in the hands. Obviously the anoxemia resulting from lowered blood pressure and lessened cardiac output during the acute phase of the infarction is not alone sufficient to produce damaging changes in the hands or these changes would appear in the feet also. Yet, it is reasonable to suppose that an often prolonged and quite intense anoxemia adds to the nutritional disturbance and tissue anoxia in hands which are being subjected to severe vasoconstriction, and may be a determining factor in the development of the syndrome.

Comment

Up to 1940, by which time 17 of our 39 cases had been collected, we had found no reports in the literature of the disabling changes in the hands following coronary thrombosis or myocardial infarction such as those described in this paper. Shoulder pain following myocardial infarction had received considerable attention.[4, 5, 6, 7, 9] In these reports the painful condition of the shoulder is often referred to as a "periarthritis," and it is suggested that the shoulder disability may result from referred anginal pain and from voluntary or involuntary splinting of the shoulder. Several writers suggest that painful shoulders may warrant the suspicion that a myocardial infarction has occurred a short time before.

Ernstene and Kinell[9] note changes in the hands in several of their 17 cases of post-infarction shoulder pain reported in 1940. The "Remarks" for two of their cases indicate that the authors had observed changes in the hands very much like those reported in our series; their case 10 suggests the early stage of the syndrome, and case 12 resembles a later and more fully developed stage with characteristic involvement of the fingers, which these authors regard as changes due to "rheumatoid arthritis" involving the fingers.

The substance of Askey's important contribution,[10] published in 1941, was brought to our attention by a personal communication * in the spring of 1940. Askey describes "the syndrome of combined shoulder and hand disability" developing in 18 cases of cardiac infarction and four cases of longstanding angina pectoris. He describes clearly the changes in the hands that are the subject of this report, and observed thickening of the palmar aponeurosis in seven of his cases. Although he remarks that "two cases suggested that the rôle of the sympathetic nerves was predominant," he feels that "the more common type suggests merely a rather rapid development of arthritis"; he considers the hand involvement to be an extension of the syndrome of shoulder pain described by earlier writers, and places a "preëxisting arthritis" or "latent arthritis" in an important etiologic rôle. However, he gives a "sympathetic nerve disturbance" an important place in the etiology even though he does not identify the changes in the hands with the sclerodactylia encountered in certain cases of Raynaud's disease. He states that "the course of the hand disability was characteristic of neither longstanding rheumatoid arthritis nor osteo-arthritis."

In spite of some differences in the observations and in the explanations given for the development of the changes observed, Askey's observations and those reported in this paper, pursued independently and simultaneously, appear to establish these changes in the hands following myocardial infarction as a definite syndrome.

The recognition of the syndrome is becoming more frequent, as indicated by Meyer and Binswanger's [12] recent report of three cases with changes in the hands similar to those which are the subject of this paper.

Summary

1. A syndrome characterized by disabling changes in the hands, which closely resembles descriptions of sclerodactylia, may develop following myocardial infarction. The syndrome developed in 39 (21 per cent) of a series of 178 consecutive cases of acute myocardial infarction.

2. The clinical observations on the 39 cases are presented in tabular form. Four cases are reported in detail with photographs, roentgenograms of the hands, and electrocardiograms.

3. The term "post-infarction sclerodactylia" is offered as a convenient and rational name for this syndrome.

4. It is suggested that many cases showing this syndrome are at the present time classified as "rheumatoid arthritis," "atrophic arthritis," "atypical arthritis," "causalgia," etc.

5. It is suggested that the etiology of "post-infarction sclerodactylia" is anoxia of the tissues of the fingers, produced chiefly by ischemia resulting from reflex vasoconstriction of the arteries of the hand induced by cardiac pain; and that the lesser ischemic effects of arteriosclerosis of these arteries

* To Dr. F. R. Schemm, whose encouragement and interest were helpful during this study.

and the local anoxemia of the fingers which is part of the general anoxemia resulting from myocardial injury may increase the degree of the damaging tissue anoxia.

Addendum: Since this article was proofread Kehl [16] has reported six cases encountered by him of Dupuytren's contracture occurring after myocardial infarction, and he quotes Hale Powers as explaining the palmar phenomenon on the basis of irritation of the sympathetics and places it "in the same category as pulmonary hypertrophic osteoarthropathy, *scleroderma* and other trophic disturbances."

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ADJUSTMENT IN WARTIME*

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A Nation Challenged

When a peace loving nation is attacked, its citizens are called upon to make the most important adjustment of a lifetime. In total war, everyone is an important cog in his country's defense. Considerations of individual convenience and safety must be subordinated for national security. In time of peace, the various vocations and avocations offer the citizen a wide choice of useful pursuits, and independence of individual action is a sign of national vitality. However, when face to face with a national emergency, a rigorous discipline is essential to efficient military action. The energies and lives of millions must be forged into a military instrument of sufficient power to meet the invaders' challenge.

Therefore, far-reaching adjustments of an individual and national character are essential if the nation is to survive.

Defining Objectives

A clear understanding of the ideals that draw a nation into war is a powerful and necessary stimulant for all. Conflicting views of the national aim and violent disputes in the economic, business, political, and professional spheres dissipate a nation's military driving power. A house divided against itself can not stand.

In the present World War, the goal to be attained can be clearly crystallized. Indeed, it must be crystallized and kept forcefully before all of the citizens to serve as a catalyst for their continued participation in the war effort.

The Atlantic Charter is a significant document in its definition of the objectives for which the United Nations are fighting. The four freedoms as outlined in the Charter are:

1. Freedom of speech and expression.
2. Freedom of worship.
3. Freedom from want, which, translated into world terms, means equal understanding which will secure to every nation a healthy peacetime life for its inhabitants.
4. Freedom from fear, which means a reduction in armament to such a point and in such a fashion that no nation would be in a position to commit an act of aggression against any neighbor.

*Read before Regional Meeting—South Central States—of The American College of Physicians, held in New Orleans, April 16, 1943.

The opinions and assertions contained herein are those of the author and are not to be construed as those of the Navy or of the naval service at large.

These, in simple terms, define our goal, winning the approbation and participation of free men everywhere.

The doctrine of a master race, which has been a leading political and social ideal in the Prussian state since 1807 and which gradually has subordinated the more peace-loving elements of the German state, has no respect for the ideal of freedom which is the central core of our country's national existence. That the Germans have a right to their own views of national policy can not be denied; that the rest of the more than two billion people inhabiting the earth will subordinate themselves to the German will, is for the present conflict to establish. In adjusting to war, it is essential to keep objectives in the forefront.

Sources of Nation's Power

Near the close of the Civil War, Henry Thoreau pointed out that, as a nation, we had about exhausted our inherited liberty, and that the stock of passively acquired freedom was running low. Thoreau indicated that new obligations were appearing for the American citizen.

The vast extent of our nation's natural resources, development of which has brought new visions of culture and enjoyment, gives us a justified sense of pride and a certain feeling of security for the future. However, as Napoleon [1] pointed out "war is three-fourths a matter of morale; physical force and material make up the remaining one-fourth." Material is of secondary importance except in the hands of a military force emotionally stirred to great action with a religious fervor that will not fail. The pioneer spirit that brought to our shores the restless explorers of earlier days has nurtured a type of citizen with a genius for invention and utilization of resources which constitute our nation's principal heritage.

Effective Mobilization

Effective mobilization requires adequate adjustment on the part of every man, woman, and child in the direction of national defense. It requires a strict evaluation of abilities and limitations so that each unit of the population may be gainfully employed. The willingness of the citizen to place himself unreservedly at the service of his country is a direct measure of his patriotism, his interest in his nation's survival.

Morale is a fighting force which sustains men, women, and children under all types of strain. It is necessary for success in any civilian enterprise but has a life and death value in the soldier. Morale, as a fighting force, has been demonstrated by the British who lived through day to day stresses of total war.

Personnel Selection: Although the nation's manpower is, on the whole, a healthy body, misfits must be promptly screened out as a preliminary to vigorous military discipline.

Rowntree [2] has revealed that 25 per cent of the 18 and 19 year olds ex-

amined under Selective Service were found unfit for military duty in spite of the fact that they are regarded as the healthiest group in the nation. Although the major cause for rejection was eyesight which accounted for 4.5 per cent, other major causes were mental, 2.8; musculo-skeletal, 2.3; cardio-vascular, 2, and educational deficiencies, 1.9.

Thom [3] points out that of three and one-half million men examined in mobilization centers, 69,394 were rejected because of some mental aberration. The frequency of neuroses in this group reported by Thom was as follows:

1. Neurasthenia.
2. Conversion hysteria.
3. Anxiety states.
4. Psychoses.

There is no place in military action for the unfit, the defectives, the alcoholics, the syphilitics, and similar invalids. Minor physical disabilities, although disqualifying the individual from participating in military maneuvers, are no handicap for one of sound mind who is eager to be a contributing factor rather than a consumer in the nation's war effort. Scientific selection and the proper placing of men is important to avoid the development of a large-scale liability.

Even before the outbreak of the present war, the psychiatrists of our nation developed a workable prophylactic approach for the selection of candidates for the armed forces. Transfer from the free and easy civilian way of life to a strict military régime subjects individuals to certain stresses and strain. Tests have been devised whereby the stamina of the embryo soldier may be fairly satisfactorily evaluated.

Menaces to Morale: Following a review of the casualties of the first World War, Lord Horder made the statement that "war produces no new nervous disorders." The term shell-shock, so popular 20 years ago as a catch-all for innumerable forms of nervous instability, has been wisely discarded. In reality, many of these are instances of an anxiety state with histrionic demonstrations as a means of escape.

There has been an exaggerated estimate of the tendency of war to produce nervous breakdown in healthy individuals. Osler [4] pointed out that "there are some people who will never be able to stand up by themselves." It has been estimated by various observers, including Strecker,[5] that approximately 10 per cent of those eligible for military service do not have the "fighting heart." Their inabilities, however, should be identified in order that these individuals may contribute to the national effort. Someone has pointed out that the worst fighting men are often the best diggers and in the latter capacity they will be helpful in a routine way. Likewise, these men find pride in wearing the uniform and are happy in the presence of friends on their own level. Disciplinary problems in the not-so-bright men are said to be almost entirely nil.

The neurotic tendency of men can be ordinarily controlled when they are doing suitable work, and in this way those who are misfits may attain a position of usefulness elsewhere.

The inheritance of defective genes and the environmental ill effects of broken homes have created large numbers of unstable individuals. In a recent book Gillespie [4] has pointed out that the "earliest cultural factor, the family, is of great significance in the genesis of a psychoneurosis." Furthermore, he states that "the main preventive of neurosis in doctors and in professional men generally might be summed up in the phrase 'professional attitude.' The individual identifies himself with his job which becomes a pivotal value for him."

The principal menace to morale is probably ignorance of what we are fighting for today. Apathy and lethargy, regarded by the medieval church as deadly sins, may be significant preceding either a psychoneurosis or an antisocial act. The Britons have frequently remarked "we would rather be bombed than bored." Isolation from congenial surroundings has opened the door for neurosis in susceptible persons. Gregariousness, as demonstrated by the Britons, has proved to be a substantial asset in maintaining morale. Idleness is a menace, and for the skilled or unskilled, work is a stabilizing factor. Gillespie [4] maintains that the more the individual is subjected to the will of the state, the greater is the liability to panic or apathy. This was confirmed recently by a German refugee who contrasted the strong inner discipline of the Britons with that of the Germans on whom discipline was imposed by authorities from without.

Separation anxiety studied by Fairbairn [6] is universally a factor of war neurosis. The occurrence of an exaggerated degree of dependence among neurotic soldiers is widespread, and Fairbairn [6] believes that the truth is not so much that the boy craves to go home because he is ill as that he becomes ill because he craves to go home. Fairbairn [6] maintains that it is impossible to draw any real distinction between war neuroses and homesickness.

Pegge [7] is of the opinion that some of the neuroses of war differ considerably from those of peace. The circumstances of war, being emotional stimuli of unwonted intensity and suddenness, cause a symptomatology more florid, more extreme, and more essentially abnormal than do the more moderate and slowly acting circumstances of peace-time life. This degree in difference of symptoms really becomes obvious only when weighed, in each case, against the personality before breakdown. To understand neurosis is to understand personality. Pegge [7] states that the process which, in the growing up of a child, leads to the development of a healthy independent adult leaves a trail of emotional events and conflicts overcome, to the more difficult of which there may be a regressive return in times of great stress. Indeed, retrogression itself can not be considered as a pathological mechanism since it may be a signal of distress and, when promptly recognized, may be the means of saving the personality. Dependence as a mechanism may be useful

in adult life as it is in the child, but it needs be followed by a phase of wise weaning. It has been stated that the conflict, "infantile dependence" versus "adventuring into adult life," is present in everyone, normal and neurotic alike. Thus neurosis is merely a quantitative variation, at best a modification, rather than a contraindication of the normal.

Why do some soldiers break down in the face of danger whereas others do not? Fairbairn [6] states that the capacity to endure danger varies with the extent to which the individual has outgrown the stage of infantile dependence. This agrees with the notorious proneness to anxiety which characterized the child as compared with the mature adult. It is, of course, important to differentiate adolescent youngsters of 18 and 19 who have entered the service and may show certain tendencies to abnormal behavior. With wise guidance these problems are promptly cleared away.

Youthful soldiers with overprotective mothers, coming from homes in which they have been sheltered and their adolescent experiences prolonged, frequently appear as neurotic. If a lad has joined the service to escape parental discipline and finds the supervision is more strict than at home, he may develop a neurosis due to maladjustment.

Borderline cases are frequently known to family doctors, and the latter may be of assistance to the officers of induction centers in pointing out prospective soldiers who have personality disorders.

Menaces to Morale

1. Ignorance of objectives.
2. Ill health.
3. Inadequate diet.
4. Loss of sleep.
5. Continuous work without periods of rest and recreation.
6. A task for which one is unfitted.
7. Idleness.
8. Boredom.
9. Strange and new type of existence.
10. Depressing news from home, or hysterical relatives.
11. Arguments between important national groups.
12. Predisposition to neurosis.

Margins of Reserve: There is, of course, a limit to the stress and strain that anyone can stand without some evidence of temporary maladjustment. This varies with the individual and from time to time in the same person. Personality deficiencies are more likely to appear in an individual who is physically below par or who is fatigued.

The average young American is healthy in body and mind, with family and social assets which serve as useful supports in time of emergencies. Approval of family and associates in his course of action is stimulating support.

Conversely, parental reproof, lack of understanding, social castigation may reduce ability for adaptation. Many psychopathological symptoms appear as defense mechanisms as anxiety attendant upon infantile dependence.

The separation complex may affect not only the soldier, but his family as well. A clear understanding of the issues involved in global war with an appraisal of each individual's responsibilities as a citizen is an important ingredient of reserve store. The nation's margin of reserve in morale will determine its ability to survive.

Mechanisms of Adjustment: During the first World War the incidence of war neuroses varied between groups in inverse proportion to their morale. Even so-called normal soldiers may develop a transient war neurosis in circumstances in which morale has been sufficiently impaired demonstrating that emotional maturity is a matter of degree and is never absolute.

Since war is abhorrent to all, it must be presented in such a light as to allow every individual to mobilize aggressive urges in the service of the nation, as pointed out by Sillman.[8] Of importance is a profound knowledge of both social and psychological forces on the part of leaders responsible for indoctrination for war. There needs be a training of the emotions in order quickly to supply a motive force of sufficient strength to enable the soldier to face enemy fire. To persuade armies of men to work, and fight, and die effectively in destroying a vast enemy demands mature self control. Adjustment must be complete; educating Americans to the art of war must be approached with a clear understanding of the intricacies of personality and its deeper hidden reactions.

To adjust for participation in the war effort, the individual's loyalty to his nation must be intensified, and he must externalize his aggressiveness toward the enemy to complete willingness to sacrifice all if need be. There is a strong fascination for war and destruction in the Japanese mind and our enemies are kept stimulated by an overwhelming desire for world power. To combat this adequately and preserve the principles of democracy requires a very clear understanding and intense belief in those principles.

Despite America's belief in democracy Sillman[8] states that education as to its deeper meaning has been strangely lacking. In peace time, patriotism as a national attribute has not been kept in the foreground.

A condensation of many sentiments is necessary for an ideal to be intensely felt and acted upon. The more sentiments that can be centered into an idea, the stronger is that idea supported.

As pointed out by Sillman,[8] the strongest forces in the individual's personality to which democracy should appeal are religion and personal honesty. To intensify individual belief in it democracy should be related to these forces.

Democracy is derived largely from the biblical concept that every man has a soul equal before God. The high spiritual goal that an individual's impulses and ideals must be devoted to the welfare of others is derived mostly

from religious sources. It is concretely expressed in the Atlantic Charter. Furthermore, it represents a principle of national existence which is alien to the German and Japanese national minds.

Democracy needs be demonstrated as a desire to introduce spiritual values into political and social life. Without these high ideals, the tolerance and basic trust in the common man on which democracy is based could never have been developed, nor can it continue. Therefore, there needs be a clustering of religious and moral principles with democracy, in order to preserve a respect for individual life.

Furthermore, the benefits of scientific, intellectual and aesthetic creativity will be preserved in the democratic principle of freedom for which our nations stand committed to total war. In the Nazi and Japanese society there is an utter disrespect for the individual and, therefore, creative work is impossible.

A second method for intensifying loyalty is through projection and introjection. Few people can sustain beliefs or intense loyalty without external reinforcement. This mechanism can be called into play by impressing on the individual the feeling that every one is concerned with this idea and the intensity of his loyalty. The individual must be brought to realize that he is a significant link in a chain and an integral part of an important undertaking. He needs to regard himself as an example for all others. The only way of combating the terror of being isolated and overwhelmed by the vast power of the enemy is by having the nation's expectancies and reassurance focused on him, as emphasized by Sillman.[8] It is through these means that he can achieve conviction and function efficiently in the face of the overwhelming destructiveness of modern war.

Associated with the utilization of projection and introjection in securing loyalty is the use of group activities. The individual's activity and personal participation in group work and group meetings is of great value in receiving the effects of introjection. Large mass meetings are useful for intensifying loyalty.

A third method for intensifying loyalty is by pointing out clearly that democracy is a unique and fragile achievement. One of the well established methods for safeguarding the feeling of love for an object is the threat of loss. Too many people assume without evidence that there is a biological drive within man for freedom and democracy. Deeper studies of the mind reveal that man's fundamental nature tends to be inimical to democracy. The individual and the nation are faced with the extermination of the most precious social achievement of all history.

A fourth method of intensifying the individual's feeling of loyalty is related to the second major phase of education to war, namely, the externalization of aggression. This is based on the deeper significance of loyalty which is fundamentally a derivative of the parental identification the individual develops in childhood. Due to the prevalence of unconscious hos-

tility against love objects, in order to intensify affection, it is necessary that the hostility also be discharged. For maximum effectiveness this must obviously be directed against the enemy. Everything should be done to make the soldier think of himself as the protecting father of his democracy.

Complete externalization of aggression is the surest way to avoid the tendency toward internalization which may produce suicide and war neuroses. Training is needed which will produce a feeling of aggression against the enemy to the point where the danger from the enemy is completely ignored.

The fact of being an American must be carefully glorified. All emphasis must be placed on the achievements of America. It is only through the awesome respect of the American ideal that the individual can be brought freely to make the sacrifice necessary for the survival of the nation.

Acknowledgment of the individual as an American, with the obligations and privileges the term implies, will effectively externalize his aggression. There is probably no soldier as efficient as he who fights for a passionate ideal compared to which his life is of small value.

Essentials for Adjustment

1. Crystallization of aims and ideals.
2. Intensification of loyalty.
3. Externalization of aggressiveness.
4. Condensation of sentiments.
5. Use of group activities.
6. Threat of loss of freedom.
7. List crimes of enemy:
    a. Rotterdam.
    b. Lidice.
    c. Mass reprisals.
    d. Treaties as scraps of paper.
8. Demonstrate lust for war as national policy of enemy.

In total war every citizen has a contribution to make. The inability of many to qualify for active military service frees them for utilization in non-combat pursuits, industrial plants, home defense, and innumerable other activities. To fulfill the obligations of citizenship requires that these individuals likewise maintain a vigorous state of health and high morale to attain the stability that is part of their contribution.

Limited Service

Rejection from an active part in a military organization need not exclude the willing individual from making a useful contribution to the war effort. Indeed, the appointment of individuals with physical disabilities in civilian jobs, thereby freeing able bodied men for military service, constitutes a

resourceful utilization of manpower. Likewise, the women of the nation are rising magnificently to the national challenge by applying in large numbers for jobs heretofore regarded as requiring able bodied men. Women workers in industry, war plants, railroads, and numerous hazardous pursuits excite the admiration of the entire nation.

The Malingerer: A small group of the population fails completely to grasp the meaning of citizenship. They are willing to accept all of the privileges but eager to escape obligations, particularly in time of war. The malingerer in industry is well known, and the psychiatrists on induction boards are quick to spot the weakling who does not want to carry his share of the national burden. Curiously, malingerers rarely try to simulate mental disease as a means of avoiding military service. In order to be fair with this group a trial period may be advised for the purpose of straightening out minor reaction kinks. On the other hand, military authorities can not have their time engaged in nursing misfits, nor should society unload social undesirables into military service.

The Training Period

The impact of war on the civilian population precipitates a situation requiring a high degree of adaptability to a new way of life for the average American. The need for adjustment is evident. The most common basis for maladjustment is anxiety, clearly defined by Whitehead [9] as "mental uneasiness arising from fear or distress, eager desire, concern." A moderate degree of anxiety is experienced by the majority of normal individuals and may act as a driving force for effective adjustment.

Anxiety, however, may exist to such an extent as to incapacitate the individual for useful service. Anxiety may show itself as a psychosomatic constellation with functional disturbances of the major body systems; it may produce excitement with trembling, perspiration and similar effects of the autonomic nervous system; it may precipitate a vicious circle in the form of worry which vitiates the individual's ability for accomplishment.

Anxiety may likewise bring about the more vague manifestations of a neurosis such as mild depression, headache or other body aches and pains or pronounced fatigue.

Adjustment problems may arise:

1. When the individual finds himself facing an impending military career.
2. When he is separated from his family.
3. Soon after induction, especially in those lads who have never been away from home.
4. Early in the preliminary period of training.

Episodes in the experience of the embryo soldier are clearly understood by psychiatrists, but there is a pressing need for a wider knowledge on the part of the medical profession as a whole in order that adequate safeguards may be created at the appropriate time.

On entering the training period, the healthy recruit finds the new life with its variety of new experiences an interesting one and receives from his buddies stimulating support that is effective in maintaining morale. The sensitive lad often finds adjustment a painful process. However, unless there is an underlying predisposition to a neurosis, this type of recruit, as a rule, will compensate for earlier lack of experience and ultimately becomes good officer material.

Modern war is a highly specialized activity. Recruits need be classified according to their adaptability for various specialized fighting services, such as engineers, infantry, submarines, tanks, etc. In the Canadian army, the doctor draws a profile, and the Army fits the man to the job. Each recruit is classified according to the physique, upper arms, legs, hearing, eyesight, and mental stability. This system, according to Meakins,[10] has worked out satisfactorily.

Military life is an active career, and associations and duties are definitely planned by superior officers for producing vigorous and healthy soldiers with a foreknowledge of the emotional turmoil that exists in many of the lads just coming into training.

The army has established nine rehabilitation camps to redirect men who have committed non-criminal minor offenses such as absence without leave and insubordination. These men spend half a day in hard work and military drill; the remainder of the day is devoted to an educational program including military and ethical lectures using the resources of psychology. When it is deemed advisable, these men are returned to an "honor company" where they are trained substantially as regulars.

In Action

Fortunately, psychiatric military services today are so well established that frank misfits and borderline cases are for the most part screened out so that only the healthiest members from the recruited groups are subjected to active combat.

It is a curious fact, as related by many soldiers who have been in action, that minor wounds sustained in combat, far from being incapacitating, act as a stimulus to heighten individual action. On the other hand, when a fellow soldier reveals an emotional strain preceding, or in action, it has, at times, a disheartening effect on those near him if they have time for observation. Whitehead [9] points out that the principal stresses and strain under combat are minimized as the man becomes hardened to battle, as has been proved by the use of experienced troops who have been many times under fire. These stresses and strains have been classified as:

1. Noise and confusion of battle.
2. The constant threat of death.
3. Observing the destruction of fellow soldiers.
4. Exhaustion and hunger.

Exhaustion is difficult to avoid when troops must be kept on the alert and ready for action over long periods of time. The problem of hunger, which is important also in maintaining high morale is, of course, a responsibility of service and supply.

A high state of morale is essential for success in battle. The well adjusted soldier has a wholesome respect for himself as well as for his fellow man. The neurotic soldier, overburdened with an anxious sensation, may be the instrument for his own and his mates' destruction. As morale falls, neurotic tendencies come to the surface.

The Home Front

As previously noted, every individual destined for action may experience periods of anxiety, a normal component of every soldier. Coupled with the morale of the fighting unit, and of equal importance, must be the knowledge by the troops that the home front is militantly supporting his every act. Cheerful news from home and knowledge that production is at the high point, that the home community is coming through with the equipment which the fighting soldier needs, are absolutely essential in war time.

In global war, civilian morale is of equal importance to that of the military. In total war, the civilian is a part time soldier and his pursuits are divided between civilian and military duties. Strecker [11] points out that functional symptoms are comparatively rare among civilians, but that when they do occur they are essentially of the same type based on anxiety. Curiously, it is the civilians who habitually seek shelter in the deeper bombproofs, who are most affected by the fear of raids, whereas those civilians with duties connected directly with the bombing, who are active in first-aid groups, or with the fire fighters and others, will show a remarkably low percentage of neuroses. It is generally accepted that the greater the sense of individual responsibility, the less is the likelihood for an inadequate reaction, that is, the better adjusted is the individual.

Strecker [11] makes a point of two emotions which stand out prominently in the British make-up, namely, infinite patience and pity that only slowly turns to anger. The British sense of detachment is important in maintaining both civilian and military morale, but finally the key to the quiet endurance of the average Briton is the knowledge that he is a free man and today he has a positive aim.

The relatively remote geographical position of our nation, which renders it less liable to bombing such as the British Isles have experienced, has kept from the American people the emotional drive for action which appears immediately after an air attack.

A high state of civilian morale requires certain fundamental health requisites be maintained. In the presence of food rationing and round-the-clock industrial activity, the population at large needs to realize that in peace

time the individual's average daily food intake is probably twice as much as his body requires, and that rationing does not of necessity reduce physical efficiency. It is largely a state of mind.

It is of importance for industry to understand the need for adequate rest and hours of recreation for industrial workers who are driving hard while at work for utmost production. The human body is not so constituted as to be able to maintain an efficient production long hours each day seven days a week without precipitating a breakdown.

Fatigue is one of the most important problems today in civilian existence and industry, as in military life, since it has a direct bearing on the morale of everyone. Therefore, working hours and military activity need be planned, insofar as possible, to maintain optimum efficiency and minimize the precipitation of neurosis.

The Britons have demonstrated that communities may become accustomed to repeated bombings and even though large numbers of the population may appear severely ill and are brought into hospitals in a state of shock, they seem to make a prompt recovery and are fit for discharge in a very few days.

The Future's Promise

A satisfactory adjustment in time of war is facilitated by a clear understanding of the ideals the nation is fighting to maintain. War has been described as a means of resolving an intolerable situation. Lack of appreciation of this fact on the part of the public and the military may bring disaster, since it goes hand-in-hand with aversion to an all-out effort for victory.

The world is moving in new directions, and nostalgia for the good old days must give way to a driving desire for a realignment of social forces in the interest of society as a whole. Democracy, if it is to be preserved, will require a more intimate participation on the part of citizens today and tomorrow in its protection. Universal military service in the broadest sense and on the part of all able-bodied students of college and secondary school rank needs to become a national instrument and should not be regarded as compulsory, but rather as a privilege and obligation.

To shorten the present conflict with the saving of many lives, otherwise needlessly lost, there needs be a militant campaign through press, radio, pulpit and public forum to emphasize more forcefully the ideals for which we, as a nation, are fighting. Schools throughout the land may contribute immeasurably to the war effort by teaching students the real meaning of freedom, inculcating in the new life blood of the nation a burning desire to participate in the largest possible way in the movement that constitutes the war effort.

Adjustment to war on a national scale is the result of personal acceptance by every citizen of his primary obligation to his native land. The concept of the brotherhood of man with equality of opportunity for all must replace the doctrine of the master race as an instrument of nations. We are all voyagers

aboard this planet on the sea of life, and if too many rock the boat, civilization itself may be lost.

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NEUROGENIC POLYCYTHEMIA *

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INTRODUCTION

THE cause of so-called polycythemia rubra vera is at present not known. It seems possible that it is a symptom complex which future observation will classify into a number of different types.

The signs and symptoms of neurological involvement in polycythemia rubra vera occur with extreme frequency (Osler,[25] Christian,[8] Mendel,[22] Brockbank [4]), and indeed "it appears that neurologic manifestations are among the commonest symptoms in polycythemia vera" (Sloan [30]).

However, the association of polycythemia rubra vera with intracranial neoplasia is an event of the greatest rarity, and there is no detailed report in the literature of its occurring with a subtentorial tumor. The observation, therefore, of a case in the University of Chicago Clinics (G. C. and E. W.) and separately a case in St. Louis (H. S.), of instances of well marked polycythemia in which the red blood cell count returned to normal following the surgical extirpation of subtentorial tumors is worthy of publication. It is surprising that in each instance the neoplasm was a hemangioblastoma, a rare intracranial growth, though it is not clear what interpretation should be placed on this occurrence.

CASE REPORTS

Case 1. M. A., a 52 year old laborer, was referred to the University of Chicago Clinics by Dr. E. Walshe, September 19, 1940, with the complaints of weakness, headaches, constipation of one year's duration, and vomiting of three months' duration. The history was unsatisfactory because of the patient's slow mentation and confusion. The family did not prove helpful witnesses.

He was well until one year previously, when he commenced to have vertical headaches and constipation. He became increasingly weak, finally unable to stand, and six months prior to admission he took to bed. A coarse intention tremor of all the extremities developed. When attempting to walk with assistance, his legs would become stiff. In the three months prior to admission he had had three attacks of sudden projectile vomiting. His son and daughter had noted his mental slowness, but no loss of orientation or memory. He did not complain of visual disturbances.

The patient was a thin, tremulous individual with greatly retarded mentation. At times he displayed a coarse tremor of the hands. He weighed 132 pounds, and was 70 inches tall. External examination showed loose inelastic skin with marked facial rubor and congestion of the small veins of the skin and conjunctiva. The mouth was edentulous, its mucous membrane markedly reddened. The neck and thorax were

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normal. He complained of tenderness when pressure was exerted over the lower lumbar spine. The patient held his back rigid and refused to bend forward. No abnormalities were noted in the heart or lungs. No organ appeared to be enlarged within the abdomen; in particular the spleen was not enlarged to palpation or percussion. No clubbing of the fingers was present. His blood pressure varied between 158 mm. Hg systolic and 120 mm. diastolic and 170 mm. systolic and 120 mm. diastolic.

The hematological findings are given in the accompanying table (table 1).

TABLE I

Blood Findings (case 1)

Date	RBC (cu. mm.)	Hgb. gm.	WBC (cu. mm.)	Cell Vol. %	Differential, Hematocrit, etc.
9-19-40	6,830,000	23	6,600		P. 65%, lymph. 22%, monocytes 8%, eosinophiles 5%
9-24-40	7,130,000	22	6,200	68%	P. 79%, lymph. 18%, monocytes 3%, reticulocytes 0.3% MC vol. 95.3 MC Hgb. 29.3
9-26-40				68	Bl. volume 7,125 c.c. Vol./kilo 105.5 c.c. Red cell mass 4844 c.c. Vol./kilo 73.2 c.c.
9-28-40	500 c.c. blood removed				
10-1-40	6,820,000	18	7,600		
10-3-40	Operation and Transfusion of 500 c.c. whole blood				
10-4-40	6,720,000	18	9,300		
10-5-40	5,360,000	15	9,300		
10-7-40	4,840,000	14.2		46	MC Vol. 97.1 MC Hgb. 29.3
10-16-40	4,660,000	13.6		44	
12-18-40	4,660,000			41	Blood volume 5356 c.c. Vol./kilo 73.7 c.c. Red cell mass 2195 c.c. Vol./kilo 29.8 c.c.
11-7-41	4,040,000	14.0	5,200	42	Reticulocytes 0%, P. 53%, large lymph. 2%, small lymph. 32%, monocytes 11%, eosinophiles 2% Bl. volume 5124 c.c. Vol./kilo 68.3 c.c. Red cell mass 2152 c.c. Vol./kilo 28.8 c.c.

The patient was seen by the neurological service in consultation six days after admission. At that time he was disoriented. There was a bilateral papilledema of three diopters. The visual fields were full. External ocular movements were full and steady. The pupils were 3 mm. in diameter and reacted well to direct light. There was no other evidence of cranial nerve dysfunction. The tendon reflexes were active and equal, and both plantar reflexes were flexor. Sensation appeared normal. The neurologist was impressed by the great effort exerted by the patient in carrying out simple movements and bizarre tremors of the extremities on voluntary movement. It was considered that his neurological difficulties were "associated with his systemic disease," but that "he had also a great many signs of conversion hysteria."

Urinalysis showed no abnormality except for one to three white cells per high power field. The Wassermann and Kahn reactions of the blood were negative. The serum calcium was 10.4 mg. per cent, and the serum potassium 3.7 mg. per cent. The phosphatase activity of the serum was 2.6 units (normal). The total plasma proteins were 6.3 grams per cent. An electrocardiogram showed a sinus tachycardia but no other abnormalities.

A roentgenogram of the chest revealed normal lung parenchyma, but there was spectacular calcification of the mesenteric lymph nodes and osteoarthritis of the spine. Roentgenograms of the skull showed a small area of calcification within the brain substance of the right parietal lobe.

A lumbar puncture was performed. The initial pressure was 320 mm. of spinal fluid. The Pandy reaction was negative, and there were six cells per cu. mm. of spinal fluid. The total protein was 32.5 mg. per cent. The Lange curve was 0011100000.

Because of the intracranial pressure the neurosurgical service was asked to see the patient regarding the advisability of subtemporal decompression. At that time, September 30, 1940, the patient was disoriented as to time, place and person. He was unable to carry out simple mentation. His neurological findings were much the same as at the earlier examination.

Because of the history, the severe nervous manifestations, and relatively few peripheral signs of polycythemia it was suggested that ventriculography be used in order to eliminate the possibility of an intracranial neoplasm in association with the systemic disease.

On October 3, 1940, under local anesthesia, bilateral perforations were made in the occipital regions. The right ventricle was reached at a depth of 5 cm. and the left with some difficulty at 5.5 cm. Clear, colorless fluid gushed out under obviously increased pressure. Approximately 120 c.c. of ventricular fluid were removed, and 100 c.c. of air injected into the ventricular system.

Roentgenograms taken following this procedure revealed a marked symmetrical dilatation of the ventricular system including the third and fourth ventricles with a small filling defect in the latter ventricle.

The patient was immediately returned to the operating room and anesthetized with ether. The posterior fossa was explored through a curved horizontal incision in the occipital region and subperiosteal dissection of the suboccipital muscles. The bone was perforated and the opening enlarged to the foramen magnum. The dura mater was incised transversely, but in carrying the incision on the right side considerable bleeding was encountered from vessels of the cerebellum adherent to the dura mater. The dura mater was finally elevated disclosing a number of large vessels over the surface of the right cerebellar hemisphere. Upon attempting to puncture the right cerebellar hemisphere, marked resistance and profuse bleeding were encountered. The cerebellar cortex was incised and at a depth of 1 to 2 mm. a reddish encapsulated tumor covered by numerous venous channels was found. The cerebellar tissue was dissected from about the tumor, and the vessels clipped and cut as encountered. As the vessels were clipped and the blood supply cut off the tumor noticeably shrank. The tumor was attached superiorly to the torcula Herophili and extended about 4 cm. to the right. When the tumor had been dissected free on all sides except from its connection to the torcula, it was lifted from its bed, the pedicle tied and cut. Several bleeding points along the torcula were controlled by muscle stamps. After complete hemostasis the dura mater was closed. The muscles were sutured to the superior nuchal line with deknatel and the skin margins approximated with two layers of black silk.

The patient had a relatively smooth convalescence. His confusion and disorientation slowly decreased but had not entirely disappeared at the time of his discharge two weeks after operation. He was able to walk, although unsteadily and on

a wide base. His visual fields were full but the visual acuity was diminished (R. E. 6/2000; L. E. 10/20). The optic discs were still elevated 2½ diopters.

The patient returned to the out-patient department on October 30, 1940. He had no complaints. He was well oriented in all phases. His gait was still on a wide base but he walked steadily.

He has been seen on three subsequent occasions. At the time of his latest visit to the Clinics, November 7, 1941, he had no complaints except for a slight dizziness on upward gaze, which he had experienced for approximately one week. He had been working as a laborer.

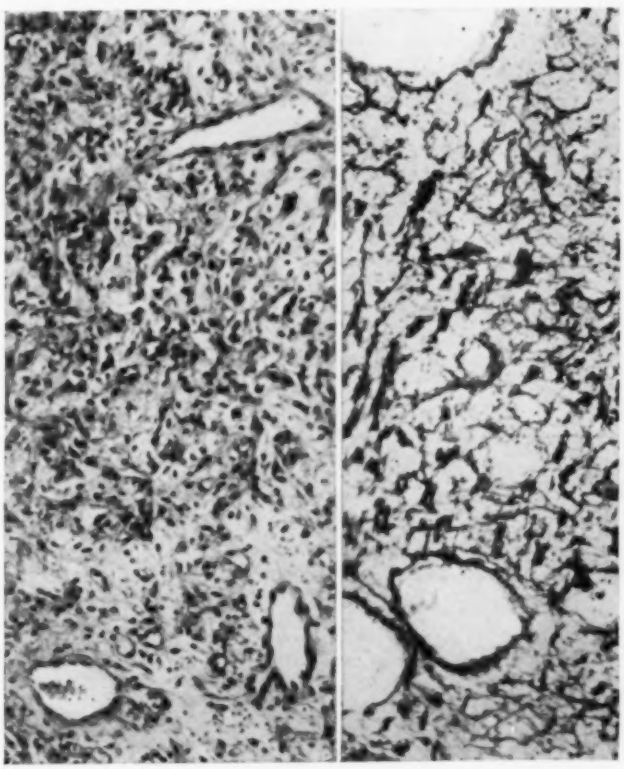

FIG. 1. Photomicrographs of sections of the tumor (case 1) stained for cells (hematoxylin and eosin) at the right and for reticulin (Perdrau) at the left (× 115).

Neurological examination at that time was normal except for the findings referable to the eyes. He could see form poorly with the right eye but with the left eye was able to read news print. Both discs were pale, flat and the margins indistinct.

Tumor. The tumor measured 3.5 by 3.5 by 2.5 cm. It was reddish brown and firm except for a cystic area about 2 cm. in diameter. Over its surface were numerous small and large blood vessels, some of which were clipped.

Microscopic examination of the tumor revealed it to be composed of closely packed capillary-like spaces lined by a single layer of endothelial cells. Between these spaces were masses of cells having round nuclei and a moderate amount of chromatin with nonstaining cytoplasm, closely resembling endothelial cells. Perdrau sections revealed an intimate network of reticulin and collagen surrounding the capillary spaces and about the cells. The tumor was a hemangioblastoma (figure 1).

Comment. From a diagnostic standpoint this case presented an interesting problem. Certainly all the findings present at the time of the clinical examination might have been the result of the polycythemia. However, the history of marked unsteadiness of gait shortly after the onset of symptoms suggested a cerebellar lesion. The marked papilledema and intracranial hypertension seemed out of proportion to what might have been expected if the intracranial disease were entirely on the basis of polycythemia.

Although hemangioblastomata of the cerebellum are frequently associated with retinal vascular malformations or angiomata, no such ocular lesion could be found on repeated examinations in the present case.

Case 2. W. Z., a 29 year old white printer, was admitted to the Deaconess Hospital, St. Louis, on March 16, 1941, on the neurological service of Dr. A. H. Deppe. He complained of headache. There was no history of weakness, vomiting, staggering gait or incoördination. Two years previously he consulted an ophthalmologist who prescribed glasses. These were worn chiefly at work. One week before admission, he again consulted his ophthalmologist, who observed papilledema of both discs and referred the patient to Dr. Deppe. Two years before the present illness, the patient had had a lymph gland removed from the region of the right nipple; according to the patient this was not malignant. Six months before admission a "cyst" was removed from the back of his neck. No details concerning this lesion could be obtained. The patient's wife had multiple sclerosis.

On admission, bilateral choked discs were noted. Neurological examination was otherwise negative, except for a questionable sensory disturbance at about the fourth cervical dermatome. A spinal puncture revealed an initial pressure of 330 mm. of

TABLE II

Blood Findings (case 2)

Date	RBC (cu. mm.)	Hgb. (gm.)	WBC (cu. mm.)	Differential, Hematocrit, etc.
3-17-41	5,960,000	18.4	9,150	Seg. 46.5%, Band 17.5%, Lymph. 32.5%, Mono. 1%, Eos. 2.5% Clotting time 3′ 15″
3-26-41	6,500,000	20	8,300	Seg. 38.5%, Band 12.5%, Lymph. 42%, Mono. 1%, Eos. 6% Platelets 295,000
3-28-41	Operation with Removal of Tumor			
4-12-41	4,390,000	13	10,950	Seg. 55.5%, Band 14%, Lymph. 30.5%, Platelets 184,900
7-17-41	6,250,000*	14.7	10,150	
7-30-41	5,100,000	17.2	6,000	P. 56%, Lymph. 25%, Mono. 7%, Eos. 10%, Reticulocytes 4%. Platelets 918,000 MC Vol. 85 MC Hgb. 31 MC Conc. 37
11-5-41	4,780,000	14.0		

* This blood count was performed by a different technician than the others in the series. The recorded red cell count is out of keeping with the recorded hemoglobin level.

spinal fluid. The Wassermann test on this fluid was negative. Roentgenograms of the skull and cervical spine showed no abnormality. The hematological findings are given in the accompanying table (table 2).

A neurological consultant on March 25, 1941 (H. G. S.) found the patient to be clear mentally, rational and coöperative. He was well-developed and well-nourished. His blood pressure was 110 mm. Hg systolic and 80 mm. diastolic. There was marked choking of both discs with complete obliteration of the disc margins, and numerous hemorrhages. The visual fields were full. The pupils were equal and reacted well, eye movements were well performed, without nystagmus. The other cranial nerves were intact. Power in all extremities was good. Fine movements were well performed. There was no ataxia or adiadochokinesis. The patient stood well in the Romberg position. The gait was normal. The tendon reflexes were active and equal on both sides. There were no pathological toe signs or clonus. No sensory disturbance could be made out.

The possibility that the polycythemia was the sole cause was considered, but the absence of other central and peripheral nervous system signs made this doubtful. Ventricular air studies were advised, to be followed by surgical extirpation of a tumor, if indicated; or, if ventriculograms were negative, it was planned to perform a subtemporal decompression to save the patient's vision.

On March 28, 1941, under avertin-local anesthesia, bilateral perforator openings were made in the parieto-occipital region. The occipital horn of the right ventricle was punctured, and about 100 c.c. of fluid were replaced with 90 c.c. of air. Films showed symmetrical dilatation of both lateral ventricles and the third ventricle.

The patient was taken back to the operating room for suboccipital craniotomy. A mastoid-to-mastoid skin incision was made. The occipital muscles were cut and stripped away from the occipital bone. The bone was then removed laterally as far as the mastoid emissary veins, and superiorly as far as the transverse sinus. After ventricular puncture to reduce pressure, the dura was opened over both cerebellar hemispheres. The occipital sinus was ligated with a transfixed suture, and cut across. The cisterna magna was completely obliterated by the cerebellar tonsils which were herniated far down into the cervical canal. The hemisphere on the left was swollen. The lamellae were flattened out, and laterally had a distinctly yellowish color. At the left lateral angle of the field several large vessels were found running from the hemisphere to the dura mater. These vessels were coagulated and cut. After coagulation of the superficial vessels, the hemisphere was incised, and the surface of a rather firm, extremely vascular tumor immediately came into view. The tumor was enucleated by blunt dissection. One large vessel running from the tumor to the petrosal sinus was coagulated and cut. The tumor was then lifted out. It had not involved the cerebellar nuclei. After removal of the tumor, in order to free the cerebellar tonsils, it was necessary to rongeur away the arch of the atlas and split the dura down to the second cervical vertebra. After complete hemostasis, the wound was closed in layers with silk sutures.

The postoperative course was uncomplicated, and the patient was discharged from the hospital on April 13, 1941, sixteen days after operation. At the time of discharge, the choked discs showed marked recession, the left fundus was normal, but the right disc margins were still blurred. Neurological examination was entirely negative. In particular, there were no signs referable to the cerebellum. On April 28, 1941, check-up examination showed very slight blurring of the right disc. One month later this had disappeared. The patient returned to work six weeks after operation. He has remained symptom-free and repeated examinations have revealed no neurological abnormalities.

Tumor. The tumor was oval in shape. It measured 3 cm. in its long axis, and 2.5 cm. in the short diameter. It was reddish-blue in color, and was of moderately firm consistency. Two large and many small blood vessels could be seen on the sur-

face. On cut surface, the color was more deeply red-brown, evidently due to blood. Microscopically, sections demonstrated tumor consisting of masses of endothelial-lined spaces within which were blood cells. There was an intimate network of reticulin. A diagnosis of hemangioblastoma was made (figure 2).

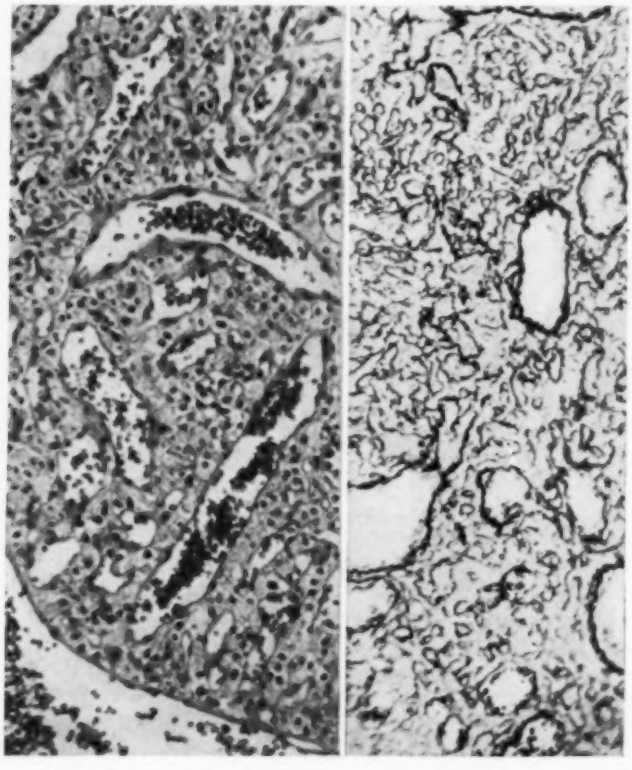

FIG. 2. Photomicrographs of sections of the tumor (case 2) stained for cells (hematoxylin and eosin) at the right and for reticulin (Perdrau) at the left (× 155). The delicate reticulin network about the cells and vessels is particularly well shown.

Comment. In this as in the first case the diagnosis was difficult and only after ventriculography could it be said with certainty that the patient had an intracranial tumor.

That the second patient had no clinical findings pointing to the cerebellum is probably due to the location of the tumor in the lateral part of the left cerebellar hemisphere without involving the cerebellar nuclei. Even large tumors in that region fail to produce cerebellar signs. Tumors situated near the midline interfering with the function of the vermis cerebelli give rise to disturbances of equilibrium such as those that initiated the first patient's illness.

It is remarked that in neither of these patients was there any evidence of dehydration which might in itself give rise to high erythrocyte counts.

In both cases the blood was examined on two or more occasions over a period of several weeks.

Discussion

It is generally conceded that intracranial lesions are frequent occurrences in polycythemia rubra vera. The common attitude toward this relationship was stated emphatically by Brockbank [4] in remarking that the nervous lesions may be regarded invariably as a function of the primary polycythemia.

However, the past two decades have seen the contribution of a small volume of literature which is devoted to the thesis that polycythemia may be due to lesions in the brain substance. It is stated (Ferraro and Sherwood [12]) that the increased incidence of encephalitis lethargica during this period, with its destruction of the vegetative centers, is directly responsible for the increased incidence of these observations.

For the most part, unfortunately, the reports of neurologic damage causally related to polycythemia do not bear critical analysis. First, the evidence of neurologic damage is based largely on clinical examinations and only in one or two cases controlled by anatomic or pathologic observations. Secondly, the blood counts submitted are often border-line and not conclusive of polycythemia, and rarely accompanied by further evidence such as blood volume studies, reticulocyte counts, and other pertinent data. Thirdly, the situation is further confused by the proximity of the pituitary gland to the vegetative centers; the occurrence of polycythemia in the course of various pituitary-adrenal syndromes (particularly the Achard-Thiers-Cushing syndrome) has been accorded general recognition during the past 10 years.

Moreover, a great number of the reports of polycythemia allegedly due to intracranial lesions come from countries bordering upon the Mediterranean basin. During the last five years it has become increasingly evident (Caminopetros,[5] Wintrobe et al.[33]) that moderate polycythemia, often with low hemoglobin values and active reticulocytosis, occurs in familial distribution in the Mediterranean races representing some forme frustre of the Cooley syndrome (Mediterranean anemia). It is to be noted, for instance, that a number of the cases presented by DaRin and Costa [9] as instances of polycythemia associated with neurologic lesions had very low hemoglobin values and reticulocytosis up to 5 per cent.

Because of these circumstances it is not proposed to give here an analytical discussion of all the reported cases in which polycythemia was the alleged result of intracranial lesions. Adequate reviews of these cases can be found in the papers of DaRin and Costa,[9] and of Ferraro and Sherwood.[12] Excluding those cases with intracranial neoplasm the greater proportion of this group suffered encephalitis, or some episode interpretable as such (Schulhof and Mathies,[29] Ceccini, Ronchetti and Gasparin,[7] Salus,[27] Riccitelli,[26] DaRin and Costa,[9] Munzer,[23] Hoff,[17] Gunther,[14] Ferraro and Sherwood,[12] and others), whereas others displayed miscellaneous causes for intracranial damage such as concussion (Hecht and Weil,[16] Guillain, Lechelle

and Garcin,[15]), Huntington's chorea (DaRin and Costa [9]), embolism (DaRin and Costa [9]), alleged central nervous system syphilis (Lhermitte and Kyriaco [19]), paralysis agitans (Ferraro and Sherwood [12]), and carbon monoxide poisoning (Dittmars [11]). From the frequency with which obesity, polyuria, and narcolepsy were seen in association with the other neurological manifestations (Kraus,[18] Munzer,[23] Gunther,[14] Salus,[27] DaRin and Costa,[9] Thiele and Bernhardt [31]) it was generally concluded that the essential lesion was in the diencephalon. But in no case in this group was anatomic evidence produced.

A small body of experimental work has been adduced to support the possible presence of a center for regulation of the erythrocyte level in the diencephalon. In 1927 Schulhof and Mathies [29] injected sclerotic agents approximately in the region of the "proximal vegetative centers" in three rabbits, in all of which there were increases in erythrocyte level of at least twice the mean deviation of counts in their normal rabbits. This report was apparently meant as preliminary, but was unfortunately never followed up with longer series, nor with anatomic studies. DaRin and Costa,[9] and Riccitelli [26] also claimed to have caused polycythemia in rabbits by damaging the diencephalic region. According to Ginsberg and Heilmeyer [13] various disturbances of the central nervous system of human beings (encephalography, lumbar puncture, concussion, epileptiform seizures) may produce reticulocytosis up to 4 per cent.

Opposite to this discussion is mention of the well controlled work of Schafer [28] in producing erythremia up to 9 million red blood cells per cu. mm. in dogs by section of all afferent depressor fibers in the cervical region. The great increase in blood volumes accompanying the polycythemia was shown to be due entirely to increase in the cell volume. Total sympathectomy abolished or prevented this effect. Hypertension with vasoconstriction is an essential part of the syndrome produced by depressor section, and it is possible that the operation presents nothing else than a surgical method of producing the type of polycythemia which Davis [10] has produced in man and animals with vasconstrictor drugs. On the other hand, its implications insofar as possible erythrocyte controlling centers are concerned cannot now be discounted. In this relation we should note that the considerable hypertension present previous to operation in case 1 (158 mm. systolic and 120 mm. diastolic; 170 mm. systolic and 120 mm. diastolic) disappeared after operation. This naturally brings to mind the possible association of this case with the type of polycythemic hypertension observed in Schafer's dogs. In case 2 no increased blood pressures were recorded.

The diagnosis of intracranial neoplasms in the presence of polycythemia may be difficult. Vascular lesions may well lead to false localizing signs, choked discs may be found (Lucas,[20] Parkes Weber [32]), and the cerebrospinal fluid pressure may reach 500 mm. of cerebrospinal fluid (Bottinger [3]). Thus, a number of cases have been explored for tumor, and none found (Christian,[8] Oppenheimer,[24] Brockbank [4]).

Relatively few reports of the association of polycythemia with intracranial neoplasms are found in the literature. A number of these neoplasms were associated with the pituitary-infundibulum, and their endocrine status cannot be established. Thus, Castex [6] reported a tumor of the hypophyseal region with a red blood count of 7,500,000 per cu. mm. DaRin and Costa [9] saw two patients with a stated diagnosis of tumor of the base of the third ventricle with counts of 5,800,000 per cu. mm. and 6,790,000 per cu. mm. respectively (in both these cases the color index was given as approximately 0.5 and the reticulocyte levels 5 per cent and 4 per cent. This raises the question of the familial hypochromia of Mediterranean peoples mentioned above). Guillain, Lechelle, and Garcin [15] reported two instances of the adipose-genital syndrome, one with diabetes mellitus, a red cell count of 6,200,000 and a "meningioma or sarcoma" of the base of the brain; the other with infantilism, a red cell count of 6,380,000 per cu. mm., with a "tumor of the pouch of Rathke." These authors reported a further case with acromegalic symptoms, enlarged sella turcica, and red cell count of 6,510,000 in which following the removal of an "adenoma of the hypophysis" the count declined to figures of 4,760,000 and 4,805,000 per cu. mm. a year after operation. (This must be regarded as probably an endocrine tumor.) Baserga [2] contributed the case of a patient with a red cell count of 6,101,000 per cu. mm., with adiposity and restriction of the temporal visual fields, in which the given diagnosis was "tumor of the hypophyseal stalk." This patient had a total blood volume of 6522 c.c.

Three cases have been described with tumors other than of the diencephalo-pituitary region. Salus's [27] patient suffered paralysis of the right arm and leg, with Jacksonian attacks, and had red blood cell counts of 6,900,000 and 6,480,000 per cu. mm. There were polyuria, glycosuria, and impotence as possible evidence of diencephalic disturbances. *At autopsy* was found a "sarcoma of the left cerebral hemisphere."

Oppenheimer [24] stated that he had "observed a case with diagnosis of polycythemia which *at autopsy* showed a cerebellar medulloblastoma." No details were given. This is the only instance in which polycythemia was said to have been associated with any type of lesion beneath the tentorium. Meiner's [21] patient had 8,500,000 red cells per cu. mm. and 138 per cent hemoglobin previous to operation on a right central degenerated glioblastoma multiforme (one of the rare instances in which a histologic diagnosis is given). Subsequent to operation normal counts were recorded, but the patient had a certain amount of diffuse roentgen-ray therapy.

In no instance of "neurogenic polycythemia" has there been described any notable enlargement of the spleen. Neither spleen nor liver was enlarged in either of our cases. This perhaps is in keeping with the conception of the erythremia as essentially symptomatic, it being widely held (though unproved) that splenic enlargement is due to the storage of cells unwanted by the circulation. From the hematologic point of view the absence of

leukocytosis and of reticulocytosis (case 1) is also in keeping with a symptomatic polycythemia.

That the pathological type of the tumor may have played an etiological rôle in the polycythemia does not seem probable in view of the fact that in a series of 14 other cerebellar hemangioblastomata none has had any evidence of erythrocythemia. Nor do Cushing and Bailey [1] mention such a complicating condition in their review of the subject.

Although it is well known that hydrocephalus due to fourth ventricle tumors does cause a dysfunction of the hypothalamic centers, it is difficult to understand the mechanism by which such a neoplasm could selectively influence one diencephalic function. And even were that possible, why should the tumors in our two cases have produced such selective alterations, and other tumors similarly situated and with equally severe hydrocephalus have failed to do so? These considerations make it difficult for us to assert a diencephalic origin of the polycythemia, although otherwise that appears to be the most likely explanation in the light of our present knowledge.

Summary

1. Two cases are reported of polycythemia which disappeared on removal of cerebellar hemangioblastomata.

2. The mechanism of this erythremia is discussed. We believe it to be of neurogenic origin.

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THE RÔLE OF CENTRAL FACTORS IN THE PATHOGENESIS OF RHEUMATIC DISORDERS *

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IN the course of development of almost any chapter of medicine there are periods when it becomes appropriate and even necessary to correlate the results of various lines of research and experience, with the aim of formulating an hypothesis as to the nature of the processes concerned, and of surveying the possibilities in new lines of approach. The field of arthritis and rheumatoid diseases is no exception to this generalization but has not often been the subject of such attempts. One reason for this is that the field as a whole has long been dominated by the view that infection accounted for it, both etiologically and therapeutically, and that other considerations were therefore largely irrelevant.

As long ago as 1920, following studies upon arthritics in the Army, one of the present writers [1] pointed out that various disturbances of physiology played a significant rôle and deserved closer scrutiny, especially as regards therapy. "There is strong evidence that infectious foci are not the only agents capable of starting a chain of events that results in rheumatism and arthritis. That this chain should be referable to one agent alone necessitates an assumption difficult of defense. It is safer, and certainly more reasonable, to believe that a variety of factors, many types of infection, exposure to cold and wet, chronic intestinal conditions of which we have only imperfect knowledge, and possibly even less ponderable glandular disturbances, may induce the substratum." This general viewpoint was long regarded in many quarters as somewhat academic except in the minds of a few close students.

There has recently arisen, however, as the result of cumulative experience, wide appreciation that the doctrine of focal infection does not operate, either etiologically or therapeutically, with such constancy as to justify the exclusive rôle formerly ascribed to it. There is, indeed, at present some danger that a negative iconoclasticism, developed in reaction to exaggerated emphasis upon the rôle of focal infection, will work injustice to countless arthritics by neglect of such focal infections as may be present and influential.

Whatever rôle may finally be ascribed to infection in the arthritic syndrome, it is fortunate that a lessened emphasis upon it has now opened the door more widely to other contemplations of the problem and indeed re-

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quires that many considerations previously waived aside be given more attention.

Any hypothesis regarding the pathogenesis of the syndrome must provide, at least, some account of the means whereby etiologic, precipitating and sustaining factors, acting either singly or synergistically, produce the full complex of physiologic deviations which characterize the disease. It is natural and appropriate that many considerations of etiologic factors have been particularly directed toward explanation of the articular features of the syndrome. The systemic nature of rheumatoid disorders, together with the generally symmetrical distribution of the major lesions, is fairly well recognized. For this reason, among others, infectious factors have been widely studied, chiefly in relation to the possible presence of infective agents or their products within articular tissues. It has been tacitly assumed that microörganisms or their toxins or both, if carried by the vascular or lymphatic routes from a focus, such as tonsils, teeth or prostate, would become equally distributed and would thus account for the important symmetrical nature of the disease so far as articular involvement is concerned.

The conspicuous failure of most efforts to isolate such suspected microorganisms [2, 3, 4] from the joints by cultural technics has led to the view that infection should be dismissed from consideration, at least practically if not academically.[5]

Similarly, guided by the principle of economy of hypothesis, traumatic factors have been studied and emphasized, primarily in respect to the influence of physical wear and tear on a single component of the articular structure, viz., cartilage.[6] It has been tacitly assumed that wear and tear on various comparable joints of the two sides of the body are essentially equivalent, except in special cases, and hence afford an adequate explanation of the frequency of symmetrical distribution of articular lesions, especially in hypertrophic arthritis. According to this view the appearance of an arthritis in mid-life is due to the summation of the total number of traumata suffered by articular tissues incidental to the passage of years. However, even limited clinical observation is sufficient to reveal incomplete correlation between the frequency and intensity of trauma and the development of articular lesions in susceptible and less susceptible persons. For example, Heberden's nodes, lesions typical of hypertrophic or osteoarthritis, frequently develop in the hands of physically inactive women, whereas such lesions are usually absent from the hands of active typists of the same chronologic age.

In addition to the foregoing considerations, which suggest the inadequacy of certain over-simplifications of the pathogenesis of arthritis, viz., that it is due to infection and trauma acting directly and alone, it is to be further observed that the actual locomotor and general disability is rarely if ever fully measurable in terms of solely articular lesions. In addition to the articular

dysfunction most arthritics present varied and unmistakable evidence of systemic deviations to be discussed later. Unfortunately no single index of systemic imbalance, when used alone, has yet been demonstrated to provide a fully satisfactory measure of the patient's general clinical condition.

The blood reflects a part of the systemic illness of the arthritic. Although there is some correlation of certain cytologic variations of the blood with the duration and type of disease,[7] these do not, when regarded separately, afford a fully satisfactory measure of the nature of the patient's illness. Anemia is frequently present and is sometimes severe, particularly in the acutely ill atrophic (rheumatoid) arthritic. This anemia is generally described as secondary, but this designation suggests that the anemia is of minor importance. However, it bears a fundamental relationship to the illness of the arthritic. This anemia is normocytic or microcytic, and the cells are hypochromic. It does not appear to be referable to an increased rate of destruction of erythrocytes inasmuch as the recticularization, icteric index and urinary excretion of urobilinogen are within normal limits. Race [8] has pointed out that the level of pigments in blood plasma is actually subnormal. The bone marrow, according to Farrar,[7] shows an increased number of normoblasts and prenormoblasts. The anemia in many arthritics responds poorly to medication with iron and liver. It may appear even more refractory than the articular disorder, remaining even after the discomfort in the joints subsides. The pathogenesis of this anemia is not fully clear. In view of the juxtaposition of certain of the pathologic processes of arthritis to the hematopoietic centers of the bone, the anemia may be regarded as a part of the syndrome. The foregoing facts suggest that an interference with the mechanism of erythropoiesis is predominant although impaired nutrition and gastrointestinal absorption may avowedly be contributory.

A "shift to the left" of the polymorphonuclear leukocytes is often observed among this class of patients. Deviations from the normal physical qualities and chemical composition of the cell-free blood fluids also occur with significant frequency. The rate of sedimentation of red blood cells in the blood plasma of many arthritics is increased, in association with an increased viscosity of the plasma. The protein fraction of blood is often abnormal. Agglutinins for hemolytic streptococci are present in high titer as well as precipitins for certain fractions of these organisms.[9] The fibrinogen of plasma and the globulin of serum are frequently elevated to high levels. The albumin fraction is sometimes considerably lowered, especially in atrophic cases of long duration and intense activity. Hypertrophics present comparable deviations but of lesser magnitude.[10, 11]

Observations on the fixed tissues from the point of view of physical and chemical constitution yield data which are equally or even more significant as compared with those presented by the circulating tissue. Muscular atrophy is evident to even a superficial examination of the rheumatoid

arthritic. Skeletal atrophy, together with atrophy of all structures of the joint, is likewise evident on roentgenographic study. Both of these features provided a basis for the designation of the term "atrophic" to the syndrome of proliferative arthritis, now designated as rheumatoid arthritis (American Committee for the Control of Rheumatism).

A low-grade peripheral edema is evident in many arthritics. Particularly conspicuous in the course of recovery is the reappearance of the interstices and tendons on the dorsum of the hand as the edema lessens and disappears. With convalescence the skin assumes an altered physical appearance characterized by apparent redundancy and fine wrinkling. During periods of clinical activity the skin over the hands, wrists, ankles, tibias and knees may be shiny as well as edematous. This sequence of changes in physical appearance is undoubtedly related to a change in the relative amounts of water in the dermal tissues.[12, 13] The nature of this peripheral edema and the several factors which modify it are not wholly evident. As regards measures influential in reducing this edema, there is evidence that nutrition, the kind of alimentation, and rest in recumbency, as well as salt intake, purgation and sweating, may play an important rôle. In addition to these factors, which may influence the ebb and flow of fluid and thereby induce exacerbations or remissions of symptoms, are the cyclic alterations in the effective levels of certain hormones. Estrogens and androgens both play rôles in the regulation of water metabolism. In addition, the adrenocortical hormones are known to be involved in the disposition of salt and water in the body. The symptoms of premenstrual tension, headache, stiffness and pain experienced by arthritic women can probably be referred to these factors.

Functional tests conducted on patients with rheumatic disorders reveal additional evidences of a departure from that "steady state" of the body as a whole, which characterizes normality. Under conditions of moderate variations in water intake, for example, there is often revealed among arthritics a decreased range of variability of renal function. Similarly gastric,[14] hepatic,[15] and gall-bladder functional tests [16] reveal departures from normal. The gastrointestinal tract as a whole is often hypotonic and its motility diminished under dietary conditions which in the normal subject afford normal function.[17]

The vascular beds of the skin are objectively modified in many of the patients who present arthritic disorders. These changes are shown by direct microscopic inspection and by skin temperature observations.[18] Few capillaries are visible and the blood flow in them is often slow and irregular. The average skin temperature is lower among many arthritics than among normal individuals subjected to the same environmental temperature. The adaptation of these patients to moderate variations in environmental temperature likewise shows a diminished and presumably less efficient range.[19]

These data suggest that the arthritic presents a multiplicity of factors which collectively underlie or constitute his illness. To attempt to show

that the complete clinical pattern presented by each patient develops from the operation of a single stimulus common to all patients would be almost a "reductio ad absurdum." It would be equally unreasonable to attempt to explain separately each congeries of deviations encountered in the arthritic as arising independently, without connection between the component parts of the full picture.

Within these broad limits, however, it is permissible to consider certain central influences, some of them operative even before the disease actually begins as a clinical entity. Data indicate that both rheumatic fever and hypertrophic arthritis occur more frequently in persons whose families present a history of rheumatic disease than among those families free from these disorders.[20, 21] There is also strong evidence to indicate that inherited susceptibility to rheumatic diseases is much greater among uniovular than among binovular twins.[22] These data tend to confirm the old concept of a rheumatic "diathesis," an inborn tendency toward the development of rheumatism. This may be more specifically described in terms of the factors constituting the "diathesis." It is assumed that the tissues of the rheumatic are more than normally susceptible to the influences of agents producing the disease. The manner in which this susceptibility develops may be classified under two main headings, viz., (1) as a consequence of body build, and (2) as a consequence of defects in local tissues. In respect to the first factor, it is generally believed that atrophic arthritis is more likely to appear in a person of asthenic type whereas hypertrophic arthritis occurs more frequently in the sthenic type. General body pattern is recognized as hereditary. In turn, it is also to be noted that differences in body build reflect differences in developmental influences. Of the recognized endogenous factors which determine rates and direction of growth, the endocrine balances are perhaps the most conspicuous. Variations in body build also involve differences in the mechanical stresses and strains imposed upon articular structures. In the sthenic individual a greater weight is supported by the joint structures than is supported by the weight-bearing tissues of the asthenic individual. It is recognized that congenital defects and anomalies occur in various organs and tissues as a resultant of endocrine dysfunction, and there is no way of disproving the possibility that moderately defective cartilage might not seem inadequate until the sum of total wear and tear exceeds the limits of this structure to withstand disintegration. Furthermore, a defective structure might break down early or later in life, depending upon the adequacy of its nutritive pabulum. The vascular supply to the region, the lymphatic drainage of the area, together with the intercellular communicating spaces, all play a rôle in determining the survival period of tissue. The effective supply of nutrients to articular regions is dynamically influenced by nervous and endocrine factors as well as by the anatomical integrity of the blood vessels. Vasomotor instability in the arthritic, already mentioned in connection with the symptoms of cold, clammy hands, may have still more deep-seated consequences. Vasomotor instability, although involving a variety of factors, may be reasonably

referred to dysfunction of the neuroendocrine system. This hereditary or congenital aspect of the matter is only one phase of the problem, however.

In addition to these features of rheumatic disease, a comparison of symptoms in experimental animals, subjected to deficiencies or excesses of pituitary factors, lends circumstantial evidence regarding the potential importance of the pituitary in relation to rheumatic disease. A general parallelism of symptoms between rheumatic patients and experimental animals subjected to hypophysectomy suggests that a common factor underlies both. The loss of the factor regulating protein metabolism following hypophysectomy in adult rats decreases the level of serum albumin and increases the level of serum globulin.[24] As noted earlier in this discussion, a corresponding deviation of serum albumin and globulin characterizes many patients with severe rheumatic disease. The changes just referred to in hypophysectomized rats show that the rise in the globulin fraction characteristic of the formation of antibodies such as develop during infection is probably not the simple humoral reaction which it has seemed to be, but is probably mediated through a central control mechanism. Although infection has been generally credited with producing this deviation as a direct response in the arthritic, it is equally conceivable that infection achieves this deviation secondarily by way of a primary influence upon the central defense mechanism of which the pituitary and associated endocrine system are a part. The rheumatic subject is abnormally sensitive to stresses of heat, cold, exercise, trauma and infections. Animals deprived of the pituitary gland are likewise in a meta-stable state [23] and respond poorly to heat, cold, exercise, trauma, infections and toxins. Asthenia is common to both the arthritic and the hypophysectomized animal.

It is not widely recognized that in addition to the local influences exerted by microörganisms upon tissues of the body per se, the presence of colonies of bacteria must divert nutrient substances from the support of essential structures. In this respect focal infection acts as a "parasitic growth," thereby producing a drain upon the nutritive resources of the host. Focal infection may indeed sometimes exercise its influences less by invasion than by extraction. The defensive reactions upon the part of the body such as leukocytosis, and the formation of humoral antibodies, involve dislocations and readjustments in body economy. The price of maintaining defense against infection is a physiological cost expressable in terms of lesser amounts of materials available for maintenance of tissues, even to the point of insufficiency. In the demands thus made, the whole chain of defense is involved. Certain of these links, however, should be considered more closely because of the recognized control which they exercise upon others. Thus, a functional insufficiency of pituitary hormones induced either by exhaustion or by direct stimulus might conceivably be comparable in its effect to anatomic absence of the gland. It appears that a part of the influence of the pituitary may be effected by way of the adrenal cortex, inasmuch as desoxycorti-

costerone prevents the change in serum proteins associated with hypophysectomy.

Other features of the rheumatic syndrome which may be attributed to a deficiency of either the adrenotropic hormone of the pituitary or the cortical hormones of the adrenal include fatigue, hypotension and lowered metabolic rate. Fatigue is conspicuous in nearly all rheumatics. Hypotension and decreased metabolic rates appear in approximately one-third of the patients in most large series of cases. Deficiency of the adrenocortical hormone might arise from hereditary insufficiency or as a secondary response to infection, toxemia or other physiological "drafts." Similarly, relative insufficiency of the thyrotropic hormone may give rise to certain of these symptoms, particularly the lowered basal metabolic rate (–15–20) and the elevated cholesterol (in hypertrophic arthritis). Cases presenting these symptoms are often benefited by appropriate doses of desiccated thyroid.[25, 26, 27, 28, 29, 30]

In contrast, Duncan [31] has described patients with articular distress associated with hyperthyroidism who have been benefited by thyroidectomy. While these data appear contradictory, this conflict may be more apparent than real. The articular manifestations may be regarded as resultants of either hyper- or hypoactivity of the thyrotropic portion of the pituitary. This situation does not represent a special case but is a general biologic function. States of dysfunction often follow successive periods of greater or lesser activity. This phasic response is well recognized in respect to the circulatory system and is also appreciated by endocrinologists.

The most direct evidence regarding the importance of the rôle of the pituitary and other endocrines in rheumatic disorders appears in women. This evidence appears in three general categories, viz., in respect to (1) the menstrual cycle, (2) pregnancy, and (3) the climacteric.

Patients with arthritis nearly always experience an exacerbation of symptoms a short time preceding the onset of menstrual flow. It appears likely that this is related to the water retention [12] occurring at this period. Underlying this, however, is the changing hormonal balance.

Chronic arthritics frequently experience a remission of active symptoms during pregnancy. This relief is so definite that Hench [32] has described patients with atrophic or rheumatoid arthritis who have become pregnant for "therapeutic purposes." One case of arthritis is on record in which a woman underwent nine pregnancies, experiencing relief in the course of each one.[32a] The metabolic activities of the pregnant woman are profoundly different from those of the non-pregnant. Endocrinous and hormonal factors are controlling elements in the situation.

Finally, a considerable number of women develop arthritic symptoms at the time of the climacteric. This occurs so frequently that a special class of rheumatic disease, designated as menopausal arthralgia, is widely recognized.[33, 34, 35] This symptom-complex may appear not only with the natural menopause but also following castration. The arthritic symptoms are often improved by the administration of estrogens. The favorable influence of

estrogens is probably not direct, but secondary to the relative depression of pituitary hormone production brought about by the estrogenic substances. Increased excretion of pituitary hormones appears following castration and the coarsening of features appearing at this time may reflect the systemic influences of increased growth factors. In illustration of this, one atrophic arthritic of 15 years' duration achieved symptomatic and longstanding arrest of a widespread symmetrical process but shortly before death developed facial symptoms suggestive of acromegaly. Osgood [34] has related the symptoms of menopausal arthritis to an increased level of pituitary substances, incidental to depletion of estrogens. Pursuing the same line of reasoning, irradiation of the pituitary has been suggested as a therapeutic measure. The principal pathologic feature of menopausal arthralgia, according to Osgood, is synovitis or degenerative joint change or both. In addition to this, Albright [36] et al. have called attention to a postmenopausal osteoporosis. This is seen in the spine and pelvis and is apparently due to failure of osteoblasts to lay down adequate organic matrix. Another pathologic feature associated with the menopause bearing upon rheumatic symptoms has been described by Kling,[37] viz., juxta-articular adiposis dolorosa with painful masses of fat near the joints. Whether this stems from pituitary dysfunction has not been demonstrated, but it appears probable in view of the similar fat dystrophy occurring in cases of pituitary disease.

Direct evidence has been presented that pituitary substances influence the growth of cartilage. Osteophytes have been produced by pituitary extracts in the spinal ligaments of dogs which are indistinguishable from those associated with degenerative (hypertrophic) joint disease.[38] Silberberg [39] has noted fibrillation of the articular cartilage of guinea pigs subjected to repeated injections of an acid extract of the anterior pituitary gland of cattle. Clinical states of acromegaly are often associated with articular lesions which bear a gross resemblance to those of hypertrophic arthritis. In addition to the articular osteophytes, splanchnomegaly or enlargement of visceral organs, together with paresthesia, occur in acromegaly. These non-articular symptoms are also presented by a number of arthritics.

In addition to symptoms referable to dysfunction of the anterior pituitary there are certain extra-articular symptoms of rheumatism which may be referable to dysfunction of the posterior pituitary. The tendency of the arthritic toward the development of a low-grade peripheral edema, described earlier in this text, may be attributed to excessive secretion of the pitressin fraction, i.e., the antidiuretic substance of the post-pituitary as well as of the gonadotropic fraction of the anterior portion of the pituitary.

Therapeutic application of the implications inherent in the foregoing considerations have been given limited but by no means complete trials. Lichtwitz [40] has advanced the view that arthritis originates from a disorder of the hypothalamic pituitary complex. Estrogens have been extensively employed in the treatment of menopausal arthralgia. Androgens have been used only occasionally in attempts to control atrophic spondylitis.[41] Some

efforts have been made to depress the growth functions of pituitary activity by the roentgen-ray. Thyroid has been used in hypothyroid and thyroidectomy in hyperthyroid arthritics with benefit not only to the thyroid condition but to the articular symptoms as well. Freyberg [42] has recently summarized a series of observations indicating limitations of hormone therapy.

In an attempt to bring the foregoing varied and numerous considerations to some sort of visual focus, however imperfect, certain of the symptoms appearing among arthritics which have counterparts in specific states of endocrine hypo- or hyperactivity are summarized in table 1. Some symptoms

TABLE I

Possible Rôle of Precipitating Factors, Acting Singly or in Combination, in Producing Symptoms of Chronic Rheumatic Disorders Through the Mediation of "Central Factors"

Precipitating or Sustaining Factors	Affecting Relative Functional Levels of Neuro-Endocrine System	Symptom Complex Resulting in the Arthritic	Type of Arthritis Involved
Infection, toxemia, hereditary imbalance, physiological "draft"; "starvation"; vitamin B complex deficiency	*Hypo* function of the *adrenotropic* factor of the pituitary or	Increased susceptibility to infection, toxins, histamine	A & H
	Adrenal cortex	Caries	A & H
		Fatigue	A & H
		Asthenia	A
		Hypotension	A
		Low BMR	A & H
	Hypo function of the *growth* factor of the pituitary	Asthenic (small stature)	A
		Secondary anemia	
		Decreasing capacity for protein synthesis	A & H
		Demineralization	A
	Hyper function of the *growth* factor of the pituitary	Osteophytes	H
		Calcification of cartilage	H
		Acral enlargement	H
		Paresthesia	
		Megacolon	H
		Sthenic (large stature)	H
Menopause	*Hypo* function of the *thyrotropic* factor of the pituitary or	"Dry" skin	H
		Low BMR	A & H
	Thyroid		
	Hyper function of the *thyrotropic* factor of the pituitary or	High BMR	
	Thyroid		
	Hypo function of the *gonadotropic* factor of the pituitary or	Arthralgia	A & H
		"Flashes"	
		Fatigue	
		Sweating	
	the gonads	Vasomotor	
		Emotional instability	
		Headache	
		Hypertension	

TABLE I—*Continued*

Precipitating or Sustaining Factors	Affecting Relative Functional Levels of Neuro-Endocrine System	Symptom Complex Resulting in the Arthritic	Type of Arthritis Involved
Pregnancy	*Hyper* function of the *gonadotropic* factor of the pituitary or Gonads	Relief of symptoms	A
	Hypo vasopressor factor of the posterior pituitary	Decreased peristalsis Low blood pressure	A & H
	Hyper-vasopressor factor of the posterior pituitary	Water retention Edema Decreased skin capillary flow	
	Nervous System		
Mechanical pressure by capsular distention, bony overgrowth, tissue swelling	Pain fibers	Pain	A & H
Nervous stress or strain from: worry, excessive activity, exposure to cold—trauma	Vegetative nervous system (1) Stimulation followed by (2) Exhaustion		
	(a) Increased adrenergic response (Epinephrine)	Peripheral vasoconstrictions Hyperglycemia Relaxation gastrointestinal tract	A & H
	(b) Increased cholinergic response (Acetylcholine)	Increased gastrointestinal tone Flushing Palpitation Sweating—general	
Exhaustion	Decreased adrenergic response	Reduced resistance to fatigue—cold Decreased BMR Poor regulation body temperature	A

are referred to imbalance in the central and in the vegetative nervous systems as well as to endocrinous factors. The separation of the vegetative nervous system from the endocrine chain may appear artificial inasmuch as these are functionally integrated. However, such a division may partially clarify the rôle of these several central factors in the pathogenesis of the multiplicity of symptoms characterizing arthritis.

Stimuli or factors such as heredity, physical activity, nutritive defects, infection, trauma and exposure may be conceived as impinging on a central mechanism. The factors comprising this mechanism are the great systems of the body, interrelated, as they are known to be, through the central nervous and endocrine chains. Many of the objective phenomena of the rheumatoid syndrome can be seen to consist of phenomena which reflect, to some extent,

supposedly normal activities of the systems concerned. It is, therefore, tempting to endeavor to relate some of these phenomena, as exhibited in disease, to under- or overaction of the systems or organs having comparable or parallel functions. No attempt to this end could be regarded with finality but it is rather surprising to observe the extent to which such an hypothesis affords a working explanation of many otherwise apparently unrelated symptoms. The symptom-complex constituting rheumatic disease, regarded in this manner, may perhaps be better described as a mesodermosis. This avoids the view that arthritis is a disorder in a single tissue produced by a solitary etiologic factor and hence amenable to a single therapeutic agent.

Development of the above hypothesis makes possible at least a tentative explanation of the alleged value of a large variety of therapeutic agents which seem to have little in common and yet, at times at least, achieve beneficial results. Under this heading can be grouped various forms of vaccines in many of which it is clear that there is no true specificity. Also to be included are such agencies as Coley's fluid, non-specific protein, bee-venom, snake-venom, typhoid injections, possibly sulphur, and also that agent which is now uppermost in the medical mind, namely, gold. The statement has been frequently made that almost any vigorous measure which is brought to bear on the arthritic, including injection of foreign substances, may achieve benefit. The injection of all of these agents induces, by definition, a greater or less defense reaction on the part of the host which may or may not express itself locally at the site of the injection. Whether or not any local antigenic reactions are developed there also takes place, by definition, a stimulation of the defense mechanism of the body as a whole in which are involved the central nervous and endocrine systems in the sense discussed above. This is perhaps most typically to be seen in the injection of typhoid vaccine in doses sufficient to induce marked fever. In such a case it is reasonable to believe that there take place so-called overflow reactions, the nature of which is in no sense specific but expresses itself widely throughout the economy. The fever is simply an end expression of the reaction and indicates the extremity to which the measure has been pushed. Less vigorous exhibitions of the same principle which do not provoke fever may, nevertheless, initiate the same general chain of defense mechanisms. Only through enlistment of central reactions can the benefits resulting from such a series of injections as is above detailed, be explained.

Summary

A survey of the clinical patterns of rheumatic disease reveals that the disorder not only affects the anatomy of articular structures but involves the functional integrity of the nervous, respiratory, neurovascular, muscular and gastrointestinal systems as well. The blood of the arthritic also presents abnormalities of its cellular and fluid components. Etiologic and sustaining factors, including infectious, traumatic, and nutritive influences, are varied

and numerous. Susceptibility of individuals to the development of rheumatic disease is greater in certain families than in others and varies with body build. These several facts may be correlated by considering the symptoms of rheumatic diseases, at least rheumatoid (atrophic) and osteo (hypertrophic) arthritis, as, primarily, direct consequences of disturbance in the several functions of the neuro-endocrine system as a whole and especially those of the pituitary gland. These disturbances of the pituitary may be determined either by congenital inadequacy or by excessive stimulation with subsequent periods of functional hyperactivity or hypoactivity. It appears unlikely that any single factor is responsible for producing the full pattern in any case.

The influences of the pituitary are perhaps most clearly operative in the so-called menopausal arthritis. The exacerbation of symptoms of stiffness and pain in an arthritic during the premenstrual phase of the reproductive cycle, and the remission of rheumatic complaints during pregnancy, although more immediately referable to gonadal activities, involve pituitary activities as well. Similarly arthralgic manifestations associated with hypothyroidism may involve pituitary factors. The states of fatigue and general asthenia characterizing many chronic arthritics could be attributed to adrenocortical insufficiency secondary to dysfunction of the pituitary. Circulatory and thermo-regulatory disturbances, seen in many arthritics and involving imbalance of the nervous system, may likewise depend upon endocrine influences initiated in the pituitary organ. Certain of the skeletal and cartilaginous defects characterizing rheumatic diseases are seen in cases of frank endocrine disease and some have been produced by pituitary substances in experimental animals.

These considerations, in addition to their theoretical interest in accounting for the symmetrical distribution of lesions and certain systemic dysfunctions, bear suggestive therapeutic corollaries which have not yet been fully explored and invite clinical as well as experimental exploitation. Nothing approaching finality of detail is here implied or intended but it is abundantly clear that any attempt at visualization of the arthritic problem as a whole must include in its purview the broad outline of the considerations here presented.

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CASE REPORTS

SUPERIOR AND INFERIOR VENAE CAVAE THROMBOSIS WITH POLYCYTHEMIA; REPORT OF A CASE *

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Thrombosis of the superior vena cava is an unusual condition, but thrombosis of both the superior and inferior venae cavae is indeed rare. In an exhaustive review of the literature in 1936 Ochsner and Dixon [1] collected 120 cases of superior vena cava thrombosis and added two of their own. Subsequently, individual cases have been reported by Szour and Berman,[2] Blasingame,[3] Buzzard,[4] and Rutledge and Gray.[5] In none of these, however, is any reference made to both superior and inferior venae cavae thrombosis.

We wish to report such a case, diagnosed antemortem and proved at autopsy, with several unusual findings not reported in other cases that warrant discussion.

Case Report

The patient, a white male, aged 42, entered the Cook County Hospital on September 9, 1940 complaining of pain in the left groin of several months' duration. He had been a moderate alcoholic for years. Physical examination revealed a left-sided inguinal hernia and a left undescended testicle. The face presented a ruddy cyanosis, and varicose veins were evident on both legs. Temperature, pulse and respiration were normal, and the blood pressure was 106 mm. Hg systolic and 90 mm. diastolic. Laboratory findings were hemoglobin 85 per cent, red cells 4,900,000 and white cells 8100. Urinalysis was negative.

Operation for the hernia and undescended testicle was performed on September 13, 1940. On the twelfth postoperative day, a large hematoma was noted at the site of the inguinal incision and on the twentieth postoperative day the base of the wound became necrotic and secondarily infected. His temperature rose to 101.2° F., and examination revealed a distended abdomen with shifting dullness. The spleen was palpable at the costal margin.

The patient was transferred to our medical service for diagnostic study on the sixty-sixth postoperative day. At this time physical examination revealed a diffuse florid cyanosis of the face, most marked in recumbency, with a peculiar puffiness of the face, especially on the right side. The superficial neck veins and the veins of the upper extremities, especially the right, were markedly distended. Varicosities of the veins of the anterior chest wall and shoulders were evident. There was also dilatation of the cutaneous venous capillaries along the right costal arch and slight edema of the right anterior chest wall and right shoulder. Heart and lungs appeared essentially normal. The abdomen was distended and there was evidence of ascites. The spleen was enlarged, being palpable about three fingers below the costal arch, and the veins on the lateral surface of the abdomen were dilated. Blood pressure was 110 mm. Hg systolic and 70 mm. diastolic, and there was slight pitting edema also of the lower extremities.

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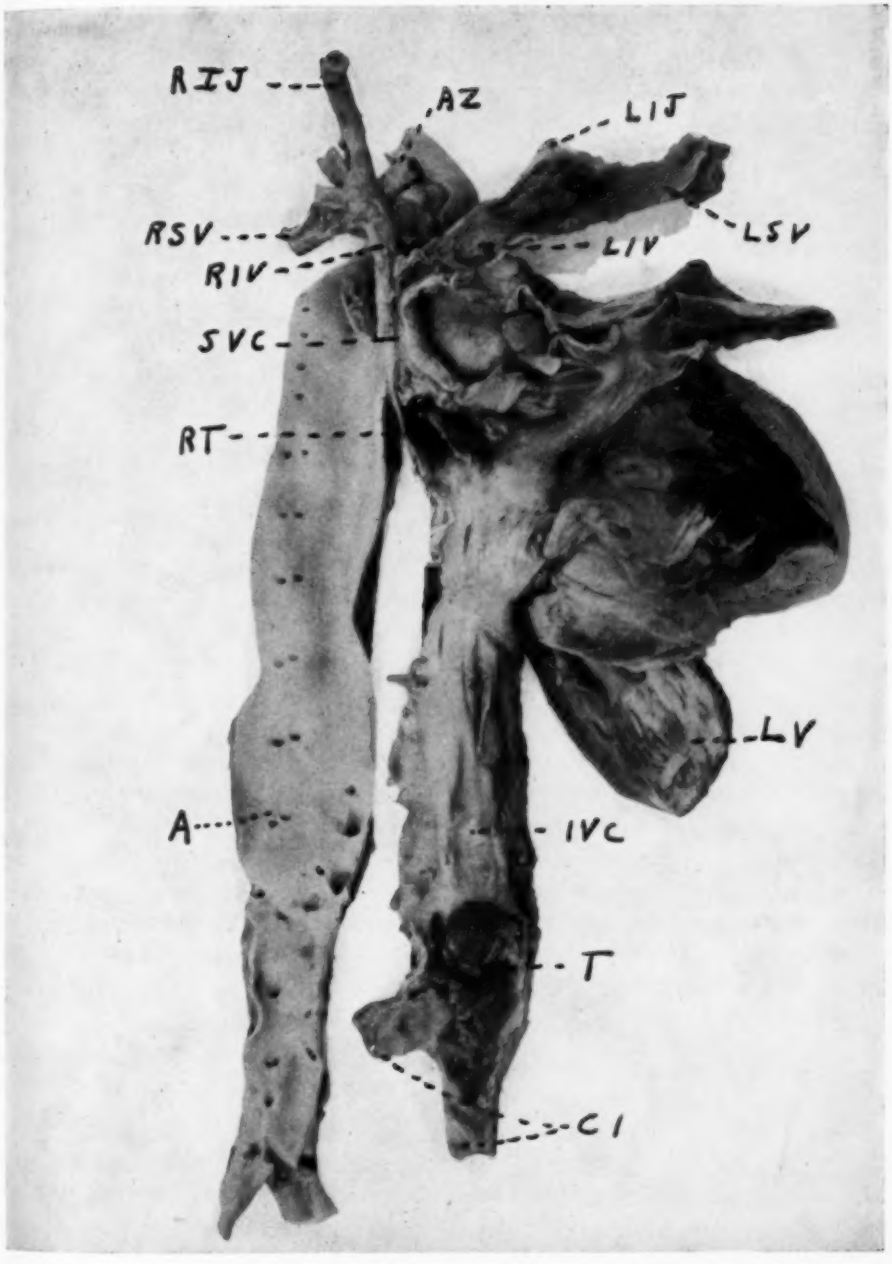

FIG. 1. A—Aorta. IVC—Inferior vena cava. LV—Left ventricle with marked fibrosis and thinning of the wall. T—Thrombus in the inferior vena cava. CI—Common iliac veins. SVC—Superior vena cava. RIV—Right innominate vein. LIV—Left innominate vein. RSV—Right subclavian vein. LSV—Left subclavian vein. RIJ—Right internal jugular vein. LIJ—Left internal jugular vein. AZ—Azygos vein. RT—Thrombus of the superior vena cava extending into the right auricle.

Studies of the peripheral blood for the first time revealed a polycythemia. Hemoglobin values varied between 98 and 100 per cent, red cell counts between 5,940,000 and 6,250,000 and white cell counts between 15,000 and 30,250 with essentially normal differential counts. A bone marrow study was essentially normal. Roentgenographic examination of the chest was negative, removing the possibility of some mediastinal mass constricting the superior vena cava, and a barium meal revealed the presence of esophageal varices. Blood chemistry studies (total protein, albumin, globulin, phosphorus, phosphatase, nonprotein nitrogen, creatinine, uric acid, etc.), although not entirely within normal ranges, were not significant. Stool specimens were positive for blood.

The patient was permitted to go home at his own request and our diagnosis at this time was superior (and inferior) venae cavae obstruction, possibly thrombosis, and secondary polycythemia with splenomegaly. Although the etiology was not certain, we felt that it was associated in some manner with the postoperative wound infection and an extensive thrombophlebitic process.

The patient returned 11 days later complaining of marked swelling of the abdomen and legs. Physical examination revealed an acutely ill and dyspneic patient with intense ruddy facial cyanosis. The superficial veins of the neck and chest wall, particularly on the right side, were markedly engorged, as were also the veins of the abdominal wall. The right side of the face and neck, the upper right arm, the right side of the chest and abdominal wall and the lower extremities revealed pitting edema. The lungs were resonant except at the bases, the heart normal, the spleen palpable, the abdomen more distended, and ascites more pronounced. The blood pressure for the first time was elevated, being 150 mm. Hg systolic and 100 mm. diastolic.

The blood count showed hemoglobin 100 per cent, red cells 7,960,000 and white cells 39,200, with 97 per cent polymorphonuclear leukocytes, 1 per cent lymphocytes, 1 per cent eosinophiles and 1 per cent basophiles, with some poikilocytosis and polychromatophilia. Blood platelets were increased.

Abdominal paracentesis yielded 8000 c.c. of a milky fluid with a specific gravity of 1.013, a 2 + protein content and 130 red and 80 white cells per cu. mm. Four days later he developed some hemoptysis and became very cyanotic and dyspneic, but was relieved by venesection of 400 c.c. blood and a second abdominal paracentesis of 7000 c.c. of a similar milky fluid.

Roentgenographic examination of the chest now revealed some encapsulated fluid in the right thorax. Repeated blood counts continued to show the picture of polycythemia and stools continually showed the presence of blood. Total blood proteins, albumin and globulin were normal; blood phosphorus was slightly increased and phosphatase activity markedly increased (11.94 units); non-protein nitrogen and icteric index were also increased.

On January 31, 1941 the patient suddenly became intensely cyanotic and dyspneic and died.

Essential Autopsy Findings. The autopsy was performed by Dr. William Mavrilus. The conjunctivae, mucosa of the lips and mouth, and the skin of the entire body, especially that of the upper extremities, head and neck, and the finger and toe nails were deeply cyanotic. The blood vessels of the neck were distended and engorged. There was pitting edema of the neck, chest, upper abdomen and upper portion of the lower extremities. The abdomen was distended two fingers above the level of the thorax. The subcutaneous tissues, especially in the neck, chest and upper abdomen, were edematous.

The abdominal cavity contained about 6500 c.c. of a light tan turbid fluid. The liver extended 2 cm. below the xiphoid process and the lower pole of the spleen was at the left costal margin at the posterior axillary line. The left pleural cavity contained 1500 c.c. of a light turbid fluid similar to that present in the abdominal cavity

and the right pleural cavity contained 1000 c.c. with focal fibrous adhesions at the lower lobe and diaphragm.

The superior vena cava was completely occluded by an organized thrombus adherent to the intima and endocardium which extended for about 3 cm. into the right auricle, upward into the right and left innominate veins and subsequently into the right and left internal jugular veins, the right and left subclavian veins and into the azygos vein. From the right auricle it extended into the right internal jugular vein for a distance of 17 cm. and into the left internal jugular vein for 8 cm. Beyond the thrombus in the left subclavian and left internal jugular veins the lumina were dilated. The adventitial tissue about the greater veins was firmly adherent to the perivascular tissue. The thrombus in the left greater vein was loosely adherent and more fibrinous than that in the right (figure 1).

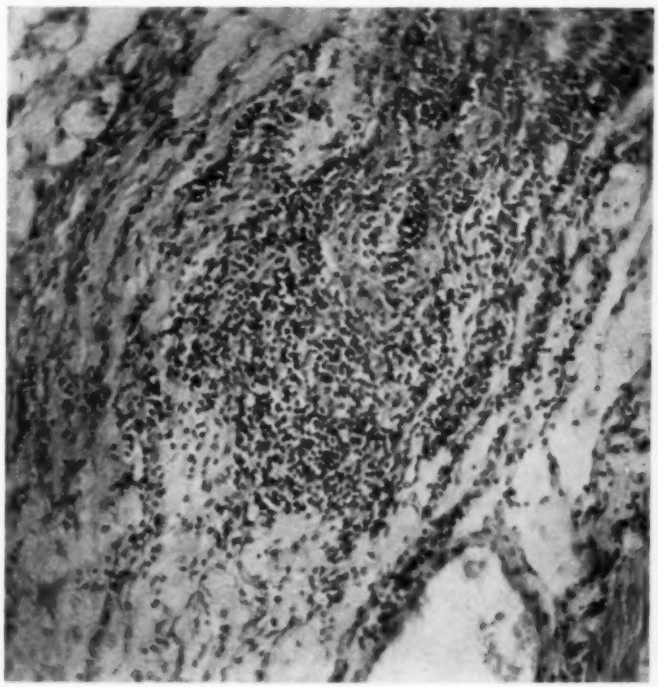

FIG. 2. Muscle and perivascular tissue of the inferior vena cava showing marked polymorphonuclear and round cell infiltration.

In the inferior vena cava about 5 cm. above the bifurcation of the common iliac veins, a purplish red thrombus, firmly attached to the intima, completely occluded the lumen. This thrombus extended upward for a distance of 5 cm., and there was a partial occlusion by a small thrombus extending downward into the left common iliac vein. Above the point of the complete occlusion the inferior vena cava was moderately dilated.

Microscopic Lesions. The superior vena cava was completely occluded by a well organized thrombus composed of collagenous fibrous tissue with round cell and polymorphonuclear infiltration, the round cells predominating. There were numerous recanalized vessels through the organized thrombus filled with erythrocytes and few leukocytes. Moderate round cell infiltration with occasional polymorpho-

nuclears was present in the media and adventitia, especially around the interstitial vessels. A similar condition was found in the right innominate, right subclavian, right internal jugular and azygos veins.

The left subclavian vein showed moderate edema of all the layers of its wall with round cell and polymorphonuclear infiltration, especially about the interstitial vessels. In the adventitia was dense infiltration of polymorphonuclear and few round cells, extending into the perivascular tissue. The lumen was partially filled with erythrocytes and leukocytes and macrophages filled with hemosiderin pigment granules.

The layers of the wall of the inferior vena cava were markedly edematous, and the interstitial blood vessels and capillaries were dilated and congested. Moderate round cell and polymorphonuclear infiltration was evident in the wall, especially around the interstitial vessels. A large thrombus, composed of fibrous tissue strands, erythrocytes, leukocytes, fibrin and platelets, was attached to the intima by newly formed capillaries and fibroblasts. The organized portion of the thrombus was infiltrated by many round and polymorphonuclear cells. This was also evident in the muscle and perivascular tissue about the inferior vena cava, especially about the small and large blood vessels (figure 2).

Discussion

We believe that the etiology of the extensive thrombotic process in this patient was the marked phlebitis with vascular and perivascular cellular infiltration, the polycythemia most probably being caused by the anoxemia which resulted from the extensive venous obstruction and pulmonary congestion.

In the cases reviewed by Ochsner and Dixon, the thrombosis resulted from phlebitis in 36.6 per cent of cases, from external compression in 29.1 per cent, and from mediastinitis in 23.3 per cent. The cause was unknown in 10.8 per cent. Of the 44 cases (36.6 per cent) resulting from phlebitis, 20 were idiopathic, 12 had syphilitic phlebitis, four tuberculous phlebitis, seven pyogenic phlebitis and one thrombotic phlebitis. Of the 20 idiopathic cases, 10 had associated heart disease. Unfortunately, these and the other reported cases give no information with regard to blood counts so that the presence or absence of a secondary polycythemia cannot be determined.

The clinical manifestations of superior vena cava thrombosis are caused by the stasis of blood in the venous tributaries draining into the superior vena cava and are limited, therefore, to the upper part of the body. This causes an increase in venous pressure in the upper half of the body and edema (due to transudation) but since collateral circulation develops, pitting generally does not occur. In our patient it did occur because of the associated thrombosis of the vessels draining into the superior vena cava. Livid cyanosis, especially of the face, results from the anoxemia due to blood stagnation, and dyspnea develops because of the slowing of local circulation with accumulation of CO_2 in the blood. Compression of the vena azygos major causes a hydrothorax and edema of the chest wall with prominence of the superficial veins due to venous stasis and increased pressure, and although this may occur bilaterally, it is generally unilateral involving the right side. The edema and cyanosis are generally increased when the patient assumes the horizontal posture. Cough is an early symptom and cerebral symptoms, such as headache, vertigo, somnolence, etc., are not uncommon because of stasis in the cerebral vessels.

If, in addition to obstruction of the superior vena cava, the inferior vena cava becomes obstructed, as occurred in our case, the lower portions of the body

become edematous and the veins distended. Thus, in our patient ascites, and edema of the abdominal wall and lower extremities were evident as well as prominence of the veins of the abdominal wall.

In the series reported by Ochsner and Dixon the mortality in the phlebitis group was 72.7 per cent. If the patient lives long enough, adequate collateral circulation may develop. This is evident in the case reported by Blasingame who observed this condition in a cadaver. The patient was a while male, aged 93, who died from cardiorenal disease and who presented no surface indications of increased venous distention. Careful dissection revealed complete thrombotic occlusion of the superior vena cava and innominate vein with partial occlusion of the subclavian and internal jugular veins and with establishment of adequate collateral circulation. Thus, the whole process appeared of long standing and was not the immediate cause of death.

In the case reported by Rutledge and Gray, the patient, male, aged 37, was operated on and the thrombus was located within the superior vena cava with a constricting band on the outside. The band (either inflammatory or congenital in origin) was cut and the thrombus was not disturbed. The patient improved after surgery and up to the time of this report was doing well. Conceivably, the thrombus became canalized. This case indicates the importance of etiologic diagnosis of superior vena cava obstruction.

SUMMARY

An unusual case of both superior and inferior venae cavae thrombosis, diagnosed antemortem and confirmed at autopsy, is reported. The etiology of the extensive thromboses in this case was most likely the postoperative phlebitis and vascular and perivascular infiltration. The associated polycythemia was a physiological secondary polycythemia due to venous stasis and anoxemia.

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HEMOCHROMATOSIS; A CASE REPORT WITH NECROPSY *

By P. A. GRAY, M.D., F.A.C.P., *Santa Barbara, California*

THE clinical features of hemochromatosis as described in Sheldon's [1] excellent monograph include (1) a predominant occurrence between 35 and 60 years of age, (2) a predilection for the male sex, (3) a familial background, (4) a short life expectancy (18½ months), and (5) a diagnostic triad of symptoms:

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pigmentation of the skin, diabetes mellitus, and cirrhosis of the liver. Butt and Wilder [2] and Lawrence [3] reported a longer survival period than this among their cases and predicted a reduction of the high mortality (50 per cent) noted by Sheldon [1] due to diabetic coma. They felt that improved treatment of the associated diabetes would improve the prognosis as regards duration of life and that death would henceforth follow the effects of the pathological changes in the liver. The present case confirms this prediction.

Few recorded cases of hemochromatosis have survived as long as the one described below. This patient lived 11 years after the diagnosis had been definitely established and about 13 years after the appearance of the first symptoms attributable to hemochromatosis. Almost all of the recorded complications of this disease eventually appeared. During life pigmentation of the skin, enlargement of the liver, and refractory diabetes mellitus were noted. Functional derangement of the liver, pancreas, heart, thyroid gland, pituitary gland, and brain appeared. At postmortem examination iron-containing pigment was found in these organs. It is believed that the fact that this patient was under continuous treatment throughout the course of his disease contributed to his unusually long survival.

Case Report

H. W. F., a male, aged 68 years, had been a mining engineer and had lived much of his life in Mexico where he had repeatedly handled copper-containing ore. He had been a life-long abstainer. When 25 years old he had had typhoid fever, followed by an appendectomy and cholecystectomy and later in the same year a pulmonary hemorrhage. Except for this series of illnesses and occasional attacks of dysentery and malaria he had remained well until 55 years of age.

The first significant symptoms noted at that time were headaches, dependent edema of the ankles, fatigue, and loss of weight. It was reported that a tender liver margin could be felt through the upper abdominal scar. A grayish color of the skin of the face was noted and upon inquiry was admitted by the patient to have been present for the preceding two years. Glycosuria was also discovered and diabetic regimen instituted. Later in the same year the patient was examined at the Mayo Clinic by Drs. Plummer, Wilder, and Allen [4] who reported a depressed basal metabolism (— 18 per cent to — 25 per cent), slate-like pigmentation of the skin, and diabetes mellitus. A biopsy of the skin confirmed the clinical impression of hemochromatosis. Shortly thereafter a definite enlargement of the liver appeared.

Throughout the rest of the patient's life he remained in Santa Barbara under continuous medical observation. His diabetes required large doses of insulin for control. One after another of his organs showed signs of insufficiency. During the last year of life his mentality failed, necessitating admission to the Psychopathic Unit of the Santa Barbara General Hospital.

The skin which originally had been unusually white, changed first to a gray, slate color, then to a muddy brown. The exposed surfaces of the face, arms, and the lower legs took on late a fine coppery sheen. Many areas of senile keratosis and purpura appeared in the bronzed areas. Early in the course of his disease his hair became dry, coarse, and white. As the disease progressed his hair gradually fell out so that he was nearly bald before death.

The liver remained tremendously enlarged for 11 years. Its size fluctuated somewhat with the degree of compensation of the circulation but always reached to the level of the umbilicus in the anterior axillary line and midway between the xiphoid and umbilicus in the midline. The liver edge was always tender and palpation of the

organ produced pain and nausea. Toward the end of the patient's life his liver became quite hard and nodular, and appeared to occupy about one-half of the abdominal cavity. The spleen also varied in size but was always palpable. It was firm but not tender. No ascites occurred.

Nasal, esophageal, and rectal varices appeared early and progressively enlarged. The corona of tremendously enlarged hemorrhoids presented a difficult, mechanical problem in defecation. Large varices of the lower extremities played a rôle in dependent edema and handicapped the healing of superficial bruises.

Electrocardiographic evidence of myocardial damage was noted six years before death. Congestive heart failure followed two years later. Thereafter circulatory compensation was maintained with difficulty by the restriction of salt and fluid intake and by the continuous administration of digitalis. The blood pressure remained about 140 to 150 mm. Hg systolic, 80 to 90 mm. diastolic.

Macrocytic, hyperchromic anemia was present for the last 10 years of life and held under control by continuous liver and iron administration. Several gastric aspirations before the esophageal varices appeared showed free hydrochloric acid present.

Asthenia and apathy were marked from the onset of his illness and were not relieved by the administration of adrenal cortex extract. Elevation of the basal metabolic rate to physiological levels by the administration of thyroid extract did not effect any clinical improvement. Libido had disappeared before coming under treatment and never reappeared. At first the patient felt cold at all times, later he felt too warm. During the last months it became difficult to keep clothes on him because he complained constantly of his skin being burning hot.

During the first three years of treatment his diabetes was readily controlled; thereafter, however, it became more difficult to control, and after the mental breakdown almost impossible. His insulin requirement remained high and fluctuated widely from day to day; yet when viewed over a period of years there was remarkable constancy. At no time during the last seven years of life was he able to do with less than 100 units of insulin daily. Sample days over a period of 11 years are shown in chart 1. Regular or crystalline insulin was used throughout. Upon each of several

CHART I

Year	Age	Weight	Diet				Insulin	Blood Sugar	Urine Sugar
			C	P	F	Cal.	RI	Mg. %	Gm.
1929	57	162	217	93	107	2303	27	70	0
1931	59	159	202	70	101	1997	59	156	9.1
1933	61	160	179	71	89	1801	181	290	19.2
1935	63	161	188	87	96	1974	173	180	+
1937	65	152	217	92	108	2208	115	238	14.3
1938	66	154	160	80	157	2373	155	266	2.4
1940	68	150	298	97	125	2695	180	158	70.0

attempts to use protamine-zinc-insulin or histone-insulin areas of induration and inflammation developed about the sites of injection. The patient complained of "electric shocks" in these areas, which raised the interesting speculation whether reaction currents were set up between the metallic ash of these insulin-preparations and the iron pigment in his skin.

This patient never required the enormous doses of insulin which have occasionally been reported among cases of hemochromatosis, yet his glycosuria could never be

completely controlled even with six injections of insulin daily. Some evidence of resistance to insulin was seen in his poor response to crystalline insulin injected intravenously under basal conditions.

Although his diabetes was not strictly controlled over a period of 11 years, the patient's resistance to infection seemed to be about normal. He recovered from two different attacks of pneumonia and from many cuts and bruises with apparently normal promptness. Urinary tract infection did not occur, and his kidney function remained normal up to the end of his life.

The capacity of this patient to react to intravenously injected insulin was tested and compared with that of a group of diabetic and non-diabetic subjects. The method used was a modification of that described previously by Gray and Burtness.[5] In all tests in this series either two or four units of crystalline insulin were injected intravenously under basal conditions regardless of the weight or age of the subject. Capillary blood sugar specimens were collected before the injection of the insulin and at 30 and 60 minutes thereafter. All specimens were analyzed by the Malmros[6] modification of the Folin-Wu technic. Results have been expressed in the milligram per cent fall of the blood sugar below the initial level per unit of insulin injected. Experience has shown that there is no significant difference in the insulin depression curves of normal subjects dependent upon the amount of insulin injected as long as the dose is kept below five units and that the maximum depression usually occurs in the 30 minute specimen. No significant difference was noted between the results obtained in this patient and those from a group of non-diabetic subjects (chart 2).

CHART II

	Number of Cases	Depression of Blood Sugar (mg. %/unit)
Subject		5.7± 2.0
Diabetic	28	11.6±11.4
Non-diabetic	51	6.9± 3.5

There was a slight difference between the patient and a group of diabetic subjects. The latter showed a somewhat greater capacity to react to intravenously administered insulin, as measured by this test, than this patient with hemochromatosis. When six times as much insulin was given to the patient as was ordinarily used for the tests done on the diabetic subjects (12 units instead of 2) an insulin depression curve was obtained which was identical with those obtained in the diabetic group when the smaller dose had been used. Hence, it was felt that some evidence of "insulin resistance" was obtained, but the degree thereof was much less than had been expected.

Necropsy Report (by Clark E. Brown, M.D.). The external examination showed the body to be that of an old white man 6 feet 1 inch tall, weighing approximately 160 pounds. The skin in general was dry and wrinkled. The head was covered with thin gray hair. The legs below the knees had a brownish color, resembling a coat of tan. The hands below the wrists were also brownish with scattered reddish-purple blotches.

The heart: all chambers appeared dilated and the ventricular musculature was flabby and brown. It had the usual thickness. The endocardium was smooth, and the valves were conspicuously delicate. The coronary arteries were soft and patent, and no atheromata were noted on multiple sections through them although roentgenogram of the postmortem specimen brought out scattered, minute calcium foci along the distribution of both branches. The arch and thoracic portions of the aorta were

smooth. The intima of the abdominal aorta contained numerous, partially calcified plaques.

The liver weighed 3910 grams. Its surface was irregularly nodular. There was a distinctly coppery color to the liver, this being more evident on the cross-section. Cut section showed the liver parenchyma separated into irregular sections by dense fibrous septi. Over the gall-bladder site were a series of yellowish white nodules, measuring up to 2 cm. in diameter. In places, hemorrhage had occurred into the nodules. In the center of this series of nodules, opaque white infiltrative hard tissue extended out into the parenchyma, giving highly suggestive evidence of an infiltrative malignant change.

The pancreas weighed 75 grams and was definitely atrophied and brownish. In the head of the pancreas there was a series of distinct opaque white nodules, the largest of which measured one centimeter in diameter (figure 1).

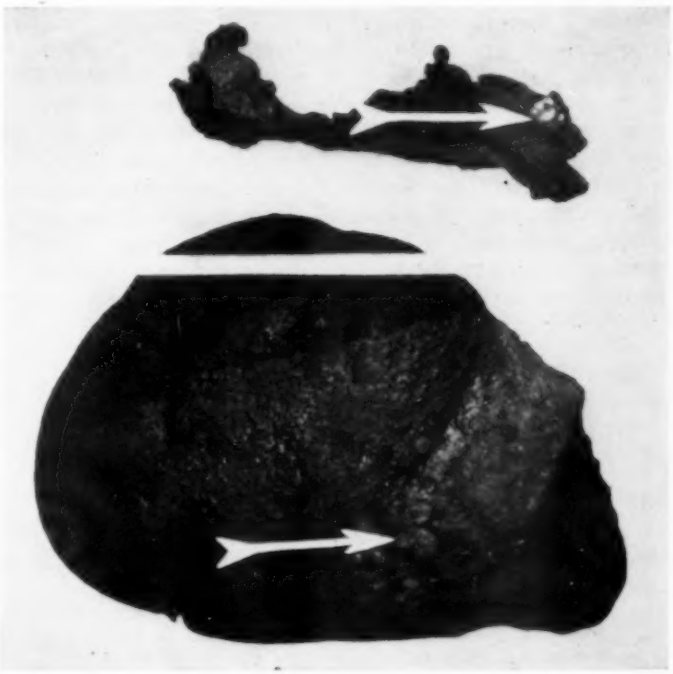

FIG. 1. Cut section of the liver and pancreas showing carcinomatous nodules. Pigment stain visible on liver surface beneath ruler.

The spleen weighed 690 grams, and had a distinct brownish hue. The kidneys weighed 230 grams each. The capsule was thin and stripped with ease. The cortex and medulla were dark and of good thickness. The adrenals weighed 21 grams. The thyroid weighed 27 grams. There were a few small cysts in one lobe. Otherwise, the parenchyma was firm and brown, and a moderate amount of colloid material was expressed from the cut surface on pressure. The parathyroids were small.

In the microscopic examination, all sections of the liver showed the lobular pattern destroyed by fine and dense bands of connective tissue. The latter contained

numerous distorted bile ducts, some of which appeared to be increased in size. Most of the liver cells contained brownish green granules of hemosiderin in their cytoplasm. Some of them were filled with small vacuoles and others were almost replaced by large vacuoles. These presumably contained fat. In one section, the irregularly divided clusters of liver cells merged with pleomorphic cells which had large hyperchromatic nuclei and rather scanty cytoplasm. A few contained hemosiderin but no bile. The Kupffer cells contained pigment, but the largest proportion of pigment was in the liver cells. The tumor cells in the liver resembled those in a lymph node situated near the head of the pancreas. The tumor cells were obviously of liver cell origin. Many of the liver cells showed various degrees of degeneration and necrosis. In parts of the tumor, zones of massive necrosis were present.

In the pancreas there was an extensive and generalized deposition of hemosiderin in the acinar tissue. The pancreatic lobules were scattered in abundant fatty tissue as though atrophy had occurred. The cells in some lobules were degenerated and there appeared to be a resultant fibrosis, both intralobular and perilobular. Islet tissue was singularly scarce. In the only two islets identified, masses of hyaline pressed against remaining islet cells with resultant atrophy. The islet cells contained hemosiderin granules. In the lymphatics in sections removed from the head of the pancreas, hepatoma cells could be seen. Hemosiderin granules were seen microscopically in the myocardium, the splenic capsule, the renai tubular epithelium, the granulosa layer of the adrenal cortex, the thyroid acini, the parathyroid cells and the skin. In the basal ganglion cells and the pars intermedia of the pituitary, pigment deposition was also seen. Some of this latter pigment resembled hemosiderin.

The anatomical diagnosis was hemochromatosis; cirrhosis of the liver with primary carcinoma, metastatic to the head of the pancreas; atrophy of the pancreas; fibrosis of the spleen and lymph nodes; myocardial degeneration; pulmonary edema; solitary cyst of the kidney; melanosis coli; gastric dilatation; and bronchopneumonia.

Summary

A case of hemochromatosis is reported in which the patient lived for at least 11 years after the diagnosis had been established by skin biopsy. All of the usual complications appeared, including insulin-refractory diabetes. Death occurred from liver damage due to pigment deposition and malignant change. Necropsy findings are reported.

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COMBINED HYPERTHYROIDISM AND ADRENAL CORTICAL INSUFFICIENCY: EFFECT OF IODINE THERAPY: A CASE REPORT *

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The coexistence of hyperthyroidism and adrenal cortical insufficiency is unusual, relatively few cases having been cited in the literature. Rolleston [1] cites several early reports of skin pigmentation in advanced Graves' disease. More recent cases have been reported, chiefly by French investigators.[2, 3, 4, 5] All these cases have been adjudged, as to the adrenal component, entirely on clinical evidences alone, and only one case of Brenner's (case 4) [6] was supported by anatomical evidence. Anderson and Lyall [7] described the appearance of Addison's disease in a patient with hyperthyroidism several years after roentgen treatment of the thyrotoxic state. The diagnosis in this instance was supported by the determination of chlorides in the blood and urine. The recent contribution of Ramos and Colombo [8] has not been available to us.

This case is reported first because of the comparative rarity of the combined states and second because of the improvement in the clinical state and changes in the blood electrolyte pattern relative to the adrenal cortical insufficiency resulting from treatment of the hyperthyroid state alone.

Case Report

On March 19, 1941, B. W., a white male aged 64, was admitted to the Beth-El Hospital complaining of urinary retention and hematuria. Three years prior to admission he had noted blood in his urine. He was told at that time that he had "stones in the bladder." Subsequently, he had polyuria, dysuria, and nocturia. For one month prior to admission severe dysuria was experienced. One week previously "clots" were noted in the urine. Four days previously the patient developed complete urinary retention accompanied by severe lower abdominal pain, and he was catheterized daily. He lost 37 pounds during the six months prior to admission; anorexia and constipation were prominent symptoms during this period.

From February 1924 until June 1925, he had been a patient at the Montefiore Hospital, treated there for chronic pulmonary tuberculosis, I A, with "fibrosis of both upper lobes, left more than right. Sputum from the time of his admission until his discharge was persistently negative. Blood pressure was 130 mm. Hg systolic and 90 mm. diastolic. There is no record of any disease of the thyroid or adrenal gland." [9]

Between 1928 and 1939 he had been intermittently treated in the out-patient department of the Jewish Hospital of Brooklyn for dysuria, hematuria, dyspnea on rest and exertion, and exertional precordial pain. Physical examinations, cystoscopy, and roentgenographic examinations of the chest and urinary tract were negative. Electrocardiograms (repeated) were normal except for low voltage. Blood pressures varied between 130 mm. Hg systolic and 80 mm. diastolic and 130 mm. systolic and 100 mm. diastolic. He was there considered to be suffering from asthmatic bronchitis, coronary sclerosis, and angina pectoris, with a cardiac classification of II B.

On admission, the patient was emaciated, anemic, complained of lower abdominal pain and appeared acutely ill. The tongue was dry and coated. The thyroid gland

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was not palpable. The heart was enlarged to slightly beyond the midclavicular line; a rough systolic murmur was localized at the apex. The lungs were clear. The abdomen was soft; the bladder was distended. The prostate was hard, adenomatous and tender. Murphy sign was positive bilaterally. Temperature was 101° F., pulse 96, respirations 28. Blood pressure was 122 mm. Hg systolic and 78 mm. diastolic. Urine showed a specific gravity of 1.009–1.030, was alkaline, had albumin 2 plus, and many white blood cells, nowhere clumped. Blood count was 4.1 million erythrocytes, hemoglobin (Sahli) 75 per cent, leukocytes 18,100. Blood sugar was 97 mg. per cent, urea 13.3 mg. per cent. Kline (blood) negative, diagnostic and exclusion.

A two stage prostatectomy was performed. The pathologic lesions reported were: "(1) fibro-adenomatous hypertrophy of the prostate, (2) chronic prostatitis with multiple miliary abscesses, non-specific."

After the second stage operation, the patient complained of increased weakness. He was unable to void spontaneously. Seventeen days after this operation, the medical department was called in consultation.

The patient now appeared weak and apathetic, complained of pain in both thighs, and could move only with great difficulty. The outstretched fingers showed a fine tremor. There was no cough. The tongue was still dry and coated. The jaws were edentulous except for two decayed roots. The buccal mucosa showed several dark gray patches on each side, some circumscribed, others diffuse. There was a generalized dark pigmentation of the skin, more marked in the creases of the palm. The perianal region was almost black. No pretibial edema was present. The palpebral fissures were somewhat widened and a congenital left lateral strabismus was present. The thyroid gland was not palpable. The chest was flat, with depressed supra- and infraclavicular fossae. There was dullness and diminished breath sounds over the entire lung bed, with crackling medium-sized râles and bronchovesicular breathing in both infra- and supraclavicular spaces. Heart sounds were distant but not otherwise altered.

Temperature was 99.6° F., pulse 78, respirations 20. Blood pressure was now 94 mm. Hg systolic and 72 mm. diastolic. Weight 101½ pounds. The urine showed no abnormalities; albumin was no longer present and there was only an occasional white cell. Blood showed a mild secondary anemia. Blood serum sodium was 104 meq./liter,[10] serum potassium 22 meq./liter,[11] cholesterol 228 mg. per cent,[12] chlorides 104 meq./liter,[13] urea 17.8 mg. per cent, sugar 136 mg. per cent. Venous pressure was 14 cm. water; with pressure over the liver, 14.5 cm. Sputum treated with antiformin showed no tubercle bacilli (six examinations). Roentgenogram of the chest showed "the heart to be of normal size and contour. The hila are the seat of lymphatic thickening and the root branches are accentuated. Excepting for a tendency to fibrosis of the linear markings, there is no evidence of recent or active parenchymal infiltration or pleural involvement." The sella turcica showed no abnormalities on roentgenographic examination. There was no evidence of a substernal thyroid gland. The basal metabolic rate was plus 71 per cent. Glucose tolerance (when the basal metabolic rate was plus 20 per cent) showed a fasting level of 62 mg. per cent; one hour, 166 mg. per cent; two hours, 176 mg. per cent; three hours, 168 mg. per cent; four hours, 146 mg. per cent.

During the first 12 days of treatment, the patient received sodium chloride and glucose, orally and parenterally, and a total of 10 c.c. of aqueous adrenal cortical extract (Wilson) and 10 mg. desoxycorticosterone acetate, the latter two because of his extreme asthenia. Thereafter throughout his stay in the hospital no therapy directed toward the adrenal gland was used. On the above regimen, the patient showed a slight but definite improvement; there was some increase in strength, and spontaneous voiding occurred on the second day after therapy was instituted. For the next eight days he received 15 minims of Lugol's solution daily. This was discontinued for 10 days to observe the effects of its withdrawal, and then reinstituted

at a dose of 5 minims daily. The changes in the laboratory data are illustrated graphically in figures 1 and 2 and summarized in table 1.

Under treatment with Lugol's solution the electrolytic pattern of the blood, and the basal metabolic rate showed prompt improvement. The patient's symptomatic response was just as definite but not so rapid. On discharge, the patient had regained the greater part of his strength, walked easily without pain, had a very good appetite, and had reached 114 pounds in weight. His blood pressure had risen to 102 mm. Hg systolic and 64 mm. diastolic.

During the first iodine withdrawal period, there was a stationary phase in the basal metabolic rate and cholesterol values. The serum sodium fell and the potassium rose; the chloride level was roughly parallel to that of the sodium. With continued administration of iodine, these values resumed their progress toward normal levels. The second withdrawal period showed only a change in the metabolic rate.

Discussion

The coexistence of hyperthyroidism and adrenal cortical insufficiency appears to be established by the data presented. The history of pulmonary tuberculosis, the profound asthenia coming on as it did after a surgical procedure of major proportion, the loss of weight, hypotension, dehydration, pigmentation, and the low serum sodium and high normal potassium levels tend to support the diagnosis. It is to be noted that the patient's most marked clinical improvement occurred during the period of administration of the Lugol's solution without specific therapy involving the use of sodium salts or adrenal gland preparations, even though the most marked blood pressure changes occurred during the period of the latter type of therapy (figure 2). It is further to be noted (figure 1) that the basal metabolic rate was not altered during the adrenal extract phase of therapy but was clearly lowered upon administration of iodine and rose upon its withdrawal; that, though the sodium level rose and the potassium fell slightly with the use of adrenal extract and sodium, these effects were much more pronounced during the period of iodine administration and were altered inversely when this was withdrawn.

The basal metabolic rate may be subnormal, normal, or elevated in Addison's disease.[14, 15] The exceedingly high rate in this case, and its response, as well as that of the cholesterol, to the administration of iodine and the inverse response upon its withdrawal indicate the presence of hyperthyroidism. The presence of a fine tremor in the hands, and the widened palpebral fissures are additional features in support of this.

In our case the question arises whether the adrenal condition was a true Addison's disease causing a secondary hyperplasia of the thyroid or whether a severe primary hyperthyroidism caused a functional adrenal cortical insufficiency.

Oehme [16] reported that adrenal cortex given to guinea pigs together with the thyrotropic principle of the anterior pituitary suppressed the increase of metabolism. This was contrary to the findings of Elmer, Giedosz, and Scheps.[17] Schacter,[18] working with dogs, failed to confirm Oehme's results. Marine and Baumann [19] demonstrated that incomplete destruction of the adrenal cortex of rabbits is followed by an increased production of body heat. This increase was not produced in thyroidectomized animals.[20] These results were corroborated in cats.[21] This led Marine to postulate adrenal cortical insufficiency as an important factor in the etiology of Graves' disease.[22] This theory was tested clinically by Shapiro and Marine [23] and Shapiro [24] who reported improvement

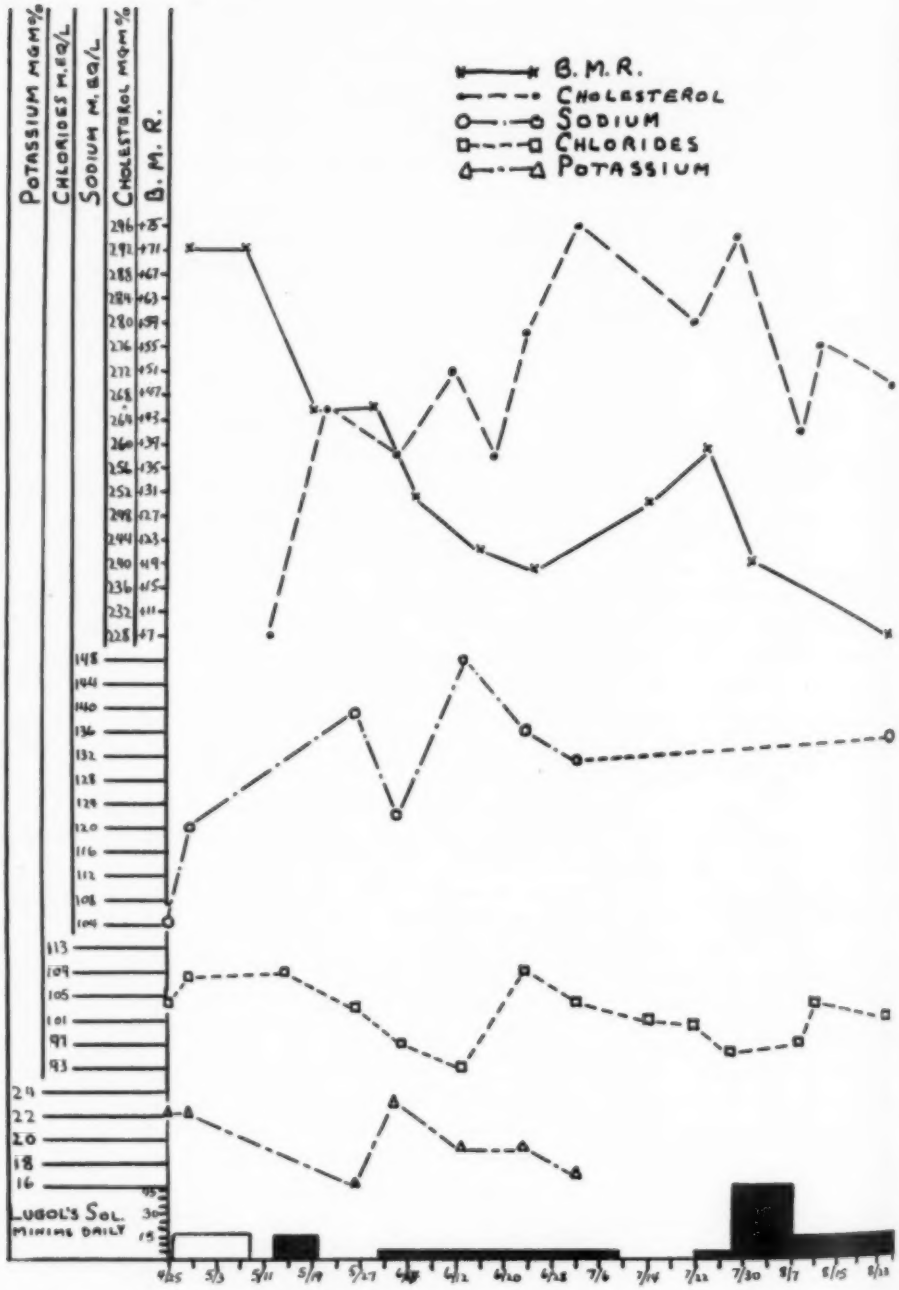

FIG. 1. Effect of Lugol's solution on blood electrolytes and cholesterol and basal metabolic rate in case of combined thyrotoxicosis and adrenal cortical insufficiency. Note that administration of Lugol's (black squares) increased cholesterol, chlorides, and sodium, and depressed potassium and basal metabolic rate, and that its withdrawal produced opposite effect. Small amounts of desoxycorticosterone (white squares) elevated sodium and slightly chlorides but produced no other changes.

of patients suffering from Graves' disease upon the administration of adrenal cortex. This work was not confirmed by the careful investigations of Weinstein and Marlow.[25]

In the light of Marine and Baumann's work, our patient might be considered a clinical counterpart of the experimental rabbit. The possibility that the adrenal cortical insufficiency was the cause of the thyroid hyperplasia cannot be defi-

FIG. 2. Effect of Lugol's solution on blood pressure and body weight in case of combined thyrotoxicosis and adrenal cortical insufficiency. Note that, while desoxycorticosterone (white squares) caused the greatest systolic rise, this had returned to original subnormal level during its administration, as did the weight. On Lugol's solution (black squares) blood pressure rise and weight increase were more moderate but sustained.

nitely ruled out. Against this view, however, may be advanced the arguments that experimental chronic adrenal insufficiency is not characterized by an increased basal metabolic rate, the reverse, in fact, being true; the rare incidence of hyperthyroidism in Addison's disease; the response of the blood electrolytes to thyroidal therapy and their maintenance in normal pattern without specific adrenal extract therapy in the case described as noted above.

The mechanism of the maintenance of the blood electrolytes within the normal range is obscure. A possible explanation may be as follows: The adrenals, presumably damaged by a tuberculous process in this case, had a decreased "reserve," of a subclinical grade. The greatly increased metabolism, the result of the increased thyroidal activity, demanded an increased secretion from the adrenal cortex beyond its reserve, as a result of which the patient exhibited signs of insufficiency. With lowering of the metabolic rate as the result of the iodine therapy, the requirement for cortical hormone decreased to a level

TABLE I

Effect of Iodine Therapy on Laboratory Data in Case of Combined Thyrotoxicosis and Adrenal Cortical Insufficiency

Date	Sodium meq/l	Potassium meq/l	Chloride meq/l	Sugar mg. %	Cholesterol mg. %	Urea mg. %	B.M.R.	Remarks
3/21				97		13.3		
4/21				93		14.6		
4/25	104	22	104	136		17.8		100 gm. glucose
4/28	120	22	108	96		9.4	+71	4 c.c. adrenal extract, 34 gm. saline
5/8							+71	Specific therapy discontinued
5/12					228			
5/14			109					Lugol's 15 minims daily begun
5/19							+44	
5/21					226			
5/26	139	16.1	103					Lugol's discontinued
5/29							+45	
6/2	122	23.2	97		258			Lugol's 5 minims daily begun 5/30
6/5							+30.2	
6/11					272			
6/13	148	19	93	89		12.6		
6/16							+21	
6/18					258			
6/23	136	19.6	109		278			
6/25							+18	
7/2	131	16.7	104		296			
7/14			101				+29	Lugol's discontinued on 7/9
7/21			100.5		280			
7/24							+38	Lugol's 5 minims daily begun 7/22
7/28			96		294			Lugol's 45 minims daily begun
7/31							+19	
8/8			97		262			Lugol's 15 minims daily begun
8/11			103.9		276			
8/25	135	16	101		270		+ 7	

again within the limits of the adrenal reserve, with improvement for the patient, as indicated by the clinical and laboratory data.

There is evidence in the literature to support this view. Thyroid feeding to experimental animals produced adrenal hyperplasia.[26, 27, 28] Zwemer [29] showed that thyroid feeding greatly reduced the survival rate of adrenalectomized rats. This was confirmed on cats by Carr and Conner.[30] In our own case, the definite reversal in the values of serum sodium and potassium during the first iodine withdrawal period and the decreased sugar tolerance lend support to this hypothesis.

Summary

A case of combined hyperthyroidism and adrenal cortical insufficiency is described. The administration of Lugol's solution controlled the basal metabolic rate, brought the blood cholesterol and electrolytic pattern within the normal range, and produced marked improvement clinically in the symptoms of both states.

The blood electrolytes were maintained at normal levels with the use of Lugol's solution alone, and tended to revert to a subnormal pattern (low sodium, high potassium) upon withdrawal of the iodine.

The sequence of events is believed to be as follows: Hyperthyroidism caused a functional adrenal cortical insufficiency due to an increased requirement of cortical hormone and decreased "reserve," probably due to previous subclinical pathological alteration of the adrenal. Administration of iodine lowered the metabolic rate and hence the demand for cortical hormone to a level within the reserve of the gland, with consequent alleviation of the symptoms of adrenal cortical insufficiency.

We should like to express our thanks to Dr. Morris Dattelbaum for helpful suggestions throughout this study, and to Mr. Bernard Klein, chemist to the hospital, for the detailed chemical analyses.

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REPORT OF A CASE OF XANTHOMA TUBEROSUM TREATED WITH LIPOCAIC*

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SEVERE disorders of fat metabolism are not extremely rare and the following case report is not submitted because of the rarity of the condition, but rather to relate the results of certain therapeutic efforts in this disease.

CASE REPORT

The patient was a white woman 49 years old at the time of examination in May 1939. She then complained of bright orange colored nodules on the palms of her hands, on the elbows, feet, knees and other areas of the skin which were frequently

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irritated by friction. This condition was of about four years' duration and was becoming more extensive. It had been noticed soon after a series of roentgen-ray treatments for a fibroid tumor of the uterus. She had not menstruated since this therapy, but had no other symptoms suggestive of the menopause. She stated that she had similar skin lesions for a short time 27 years previously, during the latter months of pregnancy. This cleared up after delivery and there had been no recurrence until the onset of the present illness. About six months prior to this examination she had complained of constricting pains around the chest and had been diagnosed and treated for coronary artery disease with almost certain coronary occlusion. She also complained of constipation, gas and bloating. There was no history of jaundice or of right upper quadrant pain. There was no dyspnea, edema or chest pain at the time of this examination. The family history was negative for illnesses similar to that presented by this patient.

On physical examination she was found to be a well developed, somewhat undernourished woman. Physical examination of the heart and lungs was normal. The outstanding finding consisted of conglomerate but not confluent masses of bright orange pigment in the skin of the palms, elbows, heels, knees and dorsum of the feet. The lesions varied in diameter from less than a millimeter to about a centimeter. They were markedly elevated in all locations except the palms of the hands in which situation they were somewhat flatter.

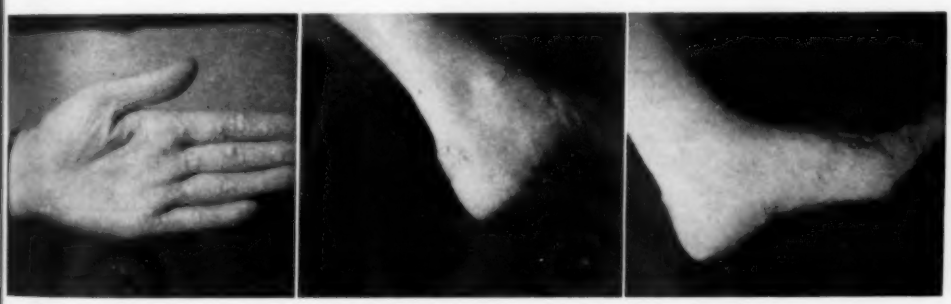

FIG. 1. Xanthomatous lesions on the extremities.

The laboratory data at the time of the original examination was as follows: Urinalysis showed a faint trace of albumin. Hemoglobin was 78 per cent. Red cell count 3.96 millions. White count 5,200 with 50 per cent adult polymorphonuclear cells, 15 per cent band cells, 2 per cent eosinophiles, 1 per cent basophiles, 4 per cent metamyelocytes, 1 per cent myelocytes and 27 per cent lymphocytes. The cell volume was 38 per cent. The sedimentation rate was 35 mm. per hour. The Wassermann, Kahn and Hinton tests were negative. The fasting blood sugar was 98.5 mg. per cent. The glucose tolerance curve was: Fasting 98.5 mg.; 30 min.—161 mg.; one hour—175 mg.; two hours—119 mg.; three hours—79 mg. This test was regarded as conclusive in excluding diabetes mellitus. The Mosenthal test showed a reduced concentrating power of the kidneys.

The initial serum cholesterol was 700 mg. and the cholesterol esters 426 mg. The chart shows the variations which occurred during 30 months of observation. The normal value for serum cholesterol may vary considerably according to different authorities; however, variations between 150 and 250 are generally considered to be normal for total cholesterol of which 40 per cent to 60 per cent is in the form of esters. It has been pointed out by Thannhauser that most of the increase in the blood cholesterol level in xanthomatosis occurs as an increase in esters. The values

for esters in the present series of tests reveals a higher proportion of esters than normal. Elevation of other blood lipids also occurs in xanthomatosis, but the increase in fatty acids and phospholipids is usually less pronounced than that of cholesterol and cholesterol esters.

The basal metabolic rate was minus 10 per cent. A roentgenogram of the heart and aorta revealed no abnormalities. Roentgenographic examination of the gall-bladder after oral administration of the dye showed normal visualization and no stones. An electrocardiogram showed the T-waves in Lead I to be of low voltage. The T-waves in Lead III were inverted. The S–T segment in Lead II was somewhat depressed. No more definite evidences of coronary artery disease were seen at this time.

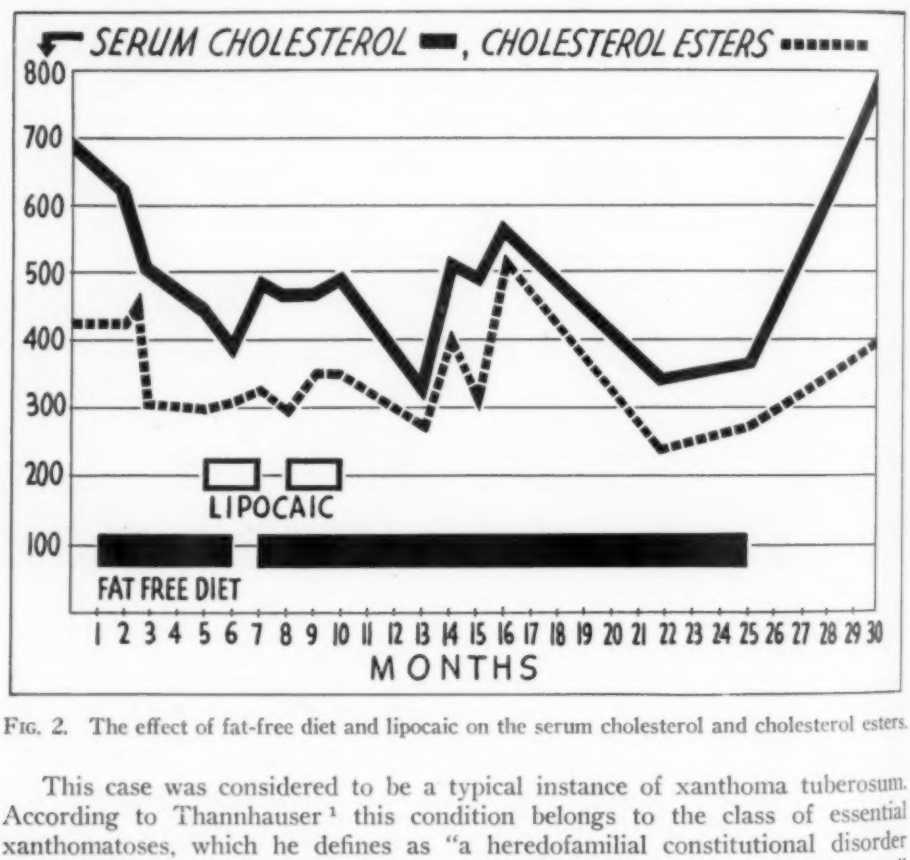

FIG. 2. The effect of fat-free diet and lipocaic on the serum cholesterol and cholesterol esters.

This case was considered to be a typical instance of xanthoma tuberosum. According to Thannhauser [1] this condition belongs to the class of essential xanthomatoses, which he defines as "a heredofamilial constitutional disorder of the intracellular metabolism of reticuloendothelial elements and histiocytes." It is characterized by an increase in the cholesterol content of the cells. The cholesterol concentration in the blood may be elevated or normal. In the hypercholesteremic type the deposits tend to occur in the skin, tendons, liver, bile ducts and blood vessels. In the normocholesteremic group the bones, brain, lungs and lymph nodes may be involved. Schiller-Christian disease is an example of the latter type. No histologic difference is noted in the two types. The essential abnormality is the presence in the tissues of xanthoma cells. These are variable sized cells usually containing two nuclei and having a reticular cyto-

plasm in which there are numerous fat droplets. This fatty substance is cholesterol and cholesterol ester. The etiology of these diseases is obscure. It is the belief of Thannhauser that there is some disorder of the intracellular metabolism in the embryonal reticular cells. There are many evidences against the theory that there is a general disturbance of cholesterol metabolism; for example, the disease may occur with normal or elevated blood cholesterol and in cases treated by diet with subsequent reduction of the blood cholesterol there is no associated disappearance of the skin lesions.

The present case demonstrates the last point. The patient was placed on a low fat, low cholesterol diet. This consisted in the elimination of all animal fats such as eggs, butter, cream, and fat meats. The prompt effect of this management on the blood concentration of cholesterol is shown by the chart. No improvement in the condition of the skin was observed.

An attempt to alter further the concentration of blood fats and possibly of the cutaneous deposits was made by the oral administration of lipocaic. This drug was described by Dragstedt [2] as a pancreatic hormone which prevented the deposition of fat in the liver of depancreatized dogs. It is thought to be a hormone which plays some part in the transport and utilization of fats. Some clinical evidence of its efficiency in reducing the fat concentration in the liver in diabetes has been described. It has also been used in other disorders of fat matabolism with results that are not very convincing. The patient received 30 grains daily for two months. During this time no change was observed in the skin lesions. The serum cholesterol fell from 454 mg. to 400 mg. during the first month of this period. During the second month on lipocaic the patient was advised to return to her normal diet. This resulted in a sharp rise in the cholesterol to 493 mg. in spite of continuing the lipocaic. The strict diet was then resumed and the drug was stopped and for the next month no significant change took place. Then lipocaic was started again in doses of 45 grains daily and this was continued for the next two months with no apparent effect on the skin condition and with very little change in the cholesterol. For the next 15 months the patient was kept on the fat free diet alone except for a brief period of administration of estrogenic hormone which the patient stopped against advice. The influence of the glands of internal secretion on lipoid metabolism is not well understood. It is not considered very likely that the artificially induced menopause had anything to do with the onset of the xanthomatosis, yet a trial of estrogenic therapy was considered worth while. The patient received four injections of 10,000 international units at weekly intervals with no improvement in the skin lesions or appreciable alteration of the cholesterol concentration in the blood. The fluctuations in blood cholesterol during this period were undoubtedly due to variations in adherence to the diet. From the twenty-fifth month to the thirtieth month she did not adhere to the diet and the last serum cholesterol was 800 mg. The skin lesions gradually became more extensive and larger. No evidence of regression of the lesions was ever noted.

Another therapeutic attempt was made to influence the cutaneous lesions. Having observed apparent regression of xanthoma deposits in the bones in Schiller-Christian disease following roentgen-ray therapy it was decided to try irradiation in this case. The hands were, therefore, treated on the palmar surfaces. The dose used was 700 r of lightly filtered roentgen-ray to each hand

given in two treatments. No evidence of improvement of the skin lesions was seen following this therapy.

Comfort and Shepard [3] of the Mayo clinic report their experience with the use of lipocaic in a case of xanthomatosis with biliary cirrhosis in which hyperlipemia, skin lesions, hepato- and splenomegaly coexisted. They observed no benefits from fat free diet alone or from diet plus lipocaic.

It is concluded from this case that it is possible to lower the serum cholesterol in xanthomatosis tuberosum by exclusion of animal fats from the diet, but that this reduction of blood fats is not accompanied by improvement of the skin lesions. Lipocaic in the doses administered to this patient had no effect on either the concentration of the serum cholesterol or on the skin lesions. Roentgen-ray therapy had no apparent effect on the cutaneous deposits.

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LEUKOERYTHROBLASTIC ANEMIA WITH DIFFUSE OSTEOSCLEROSIS *

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This report is that of a case of a severe progressive anemia with osteosclerosis. The clinical picture as well as the pathological findings we deem to be of sufficient interest for detailed description.

Case Report

The patient, a male, white, born in the U. S., a clerk by occupation, was admitted to the Welfare Hospital for Chronic Diseases on November 11, 1939, with chief complaint of anemia of seven years' duration, weakness, dyspnea on exertion, and swelling of legs and scrotum.

History before admission to Welfare Hospital: In July, 1934, at the age of 52, he was advised to have 10 teeth removed; the reason is unknown. Shortly thereafter he began to complain of dyspnea on exertion and night sweats. He was also found to be anemic by a family physician.

Between July 1934 and November 1939, the following information appeared in the case history: In January, 1935, splenomegaly was discovered for which splenectomy was performed. The spleen weighed eight pounds and had multiple infarcts. Impression: "Possible Hodgkins." In October 1935, the patient complained of dyspnea, weakness, and tingling of lower extremities. Roentgenograms of the skull and right femur were negative. In April 1936, roentgenograms of femurs showed no abnor-

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malities. In October 1937, roentgenogram of the skull was negative. In February 1938, roentgenograms of the right shoulder, left hip, and skull were negative. Blood pressure was 210 mm. Hg systolic and 160 mm. diastolic. In June 1938, ascites was present. Blood pressure was 155 mm. Hg systolic and 55 mm. diastolic. In June 1939, an enlarged liver and bilateral papilledema were observed. Roentgenogram of the spine showed hypertrophic osteoarthritis. In July 1939, there was a severe hemorrhage following removal of a loose tooth. In October there was a hemorrhage from the gums; the epitrochlear lymph nodes were palpable.

For laboratory findings prior to admission to Welfare Hospital, see tables 1 and 2.

Family history: Mother died at the age of 54 of carcinoma, type unknown. Father died at the age of 70 years of heart disease. The patient had been married 30 years; there were no children.

Examination on admission to Welfare Hospital: Temperature 100.2° F., pulse 88, respiration 22. Blood pressure was 165 mm. Hg and 75 mm. diastolic. Conjunctivae were pale. The mouth and throat showed no abnormalities. The lungs were clear and resonant. Heart, apex at sixth intercostal space between mid-clavicular and anterior axillary lines. There was a soft systolic murmur at the apex. The pulmonic second sound was louder than the aortic second. Regular sinus rhythm. There was a mass in the upper abdomen, apparently liver, with lower edge palpable four fingers below costal margin. A longitudinal scar was present on the left upper quadrant of the abdomen. A few small epitrochlear glands were present. The skin was gray and dry.

Blood picture: see table 3.

Laboratory findings: See table 4.

Résumé of roentgenographic findings (reported by Dr. Henry K. Taylor): The skull, spine, ribs, pelvis, and practically all the long bones showed a generalized increase in density with no morphological alterations in structure or contour.

Course in hospital: The patient frequently presented dyspnea and orthopnea while at rest. There was marked edema of both lower extremities reaching to the level of the middle of the back. He showed slight fever. On February 24, 1940 he had two severe attacks of dyspnea accompanied by a change of his cardiac rhythm to fibrillation. He developed generalized anasarca and died March 6, 1940.

Autopsy: The autopsy was performed 16 hours after death.

External examination: Marked generalized anasarca, skin pale and slate blue in color. No petechiae or hemorrhages present.

Chest: Bilateral pleural effusions, left 750 c.c., right 850 c.c.; fluid was turbid with a greenish tint, contained fibrin flakes. Specific gravity was 1.012, cell count 500 per cu. mm. There was marked edema of both lungs, and congestion of both lower lobes.

Heart: Pericardial cavity contained 320 c.c. of turbid greenish fluid containing fibrin. Specific gravity was 1.013, cell count 600 per cu. mm. The heart was globular, enlarged to right and left, weight 650 grams, flabby. Left ventricle was 18 mm. thick, right ventricle 7 mm. The myocardium was pale. The mitral leaflets were slightly thickened. Small friable vegetations were present on the line of closure. There was slight hypertrophy of the papillary muscles of the left ventricle. The pulmonic and tricuspid valves were normal. On the ventricular surface of aortic leaflets, small vegetations, 1 to 5 mm. in diameter, friable and white gray in color, were present. Cusps were normal. Coronary arteries were patent, and showed a few atheromatous plaques. Aorta showed slight atheromata.

Abdomen: The omentum was adherent to the anterior abdominal wall at the site of the postoperative scar. 2200 c.c. of greenish turbid fluid were removed. Specific gravity was 1.014, cell count 600 per cu. mm.

The liver weighed 3900 grams. There were fibrin deposits on the surface. On

TABLE I

Blood Picture (Before Admission to Welfare Hospital)

Date	Hgb.	R.B.C.	W.B.C.	Myelo-blasts	Myelo-cytes	Meta-myelo-cytes	Mature			Lymph.	Mono.	Miscellaneous	Remarks
							N	E	B				
Jan. 1935	86%	4,350,000											Following splenectomy
Nov. 1935	78%	4,150,000	44,810										Following transfusion
Apr. 1936	25%												
Apr. 1936	54%												Following transfusion
Jan. 1937	30%												
Jan. 1937	57%												Following transfusion
Aug. 1937	44%	2,930,000											
Aug. 1937	69%	4,200,000											
Oct. 1937													Diagnosis "erythro-blastic anemia"
June, 1938	37%	2,300,000	80,000		37		11			5		Normoblasts 43 Unclassified 4	
July, 1939	55%	2,650,000											Following transfusion
July, 1939	42.7	2,430,000	9,100			32	43	2		19	4	Reticulocytes 1.3 Normoblasts 101 per 100 w.b.c. Corrected ESR 18 M.C.V. 90 cu/m Bleeding time 1½ min. Coag. 8 min.	
Aug. 1939	40%	1,850,000											Following hemorrhage due to removal of loose tooth
Oct. 1939			13,300			18.5	45	0	.5	30.5	1	Reider 0.5 Unclassified 35 Aniso., poikilo., baso-philic stippling 17.5, normoblasts per 100 w.b.c.	

TABLE I—*Continued*

Date	Hgb.	R.B.C.	W.B.C.	Myelo-blasts	Myelo-cytes	Meta-myelo-cytes	Mature			Lymph.	Mono.	Miscellaneous	Remarks
							N	E	B				
Oct. 1939 attempted sternal puncture				1 pro-myelo-cyte	2	22	22	0	0	44	3	Reider 2 Unclassified 4 24 normoblasts per 100 w.b.c.	Resembles peripheral blood
Oct. 1939		670,000	6,430	2 pro.	2	15	32		2	40	4	Platelets 1,110,000? Plasma cell 1% 52 normoblasts per 100 w.b.c.	

TABLE II

Laboratory Data (Before Admission to Welfare Hospital)

Date	Glu.	Blood Chemistry					Miscellaneous	S.G.	Urine			Microscopic and Other	Other Tests
		N.P.N.	Urea N	Total Prot.	Alb.	Glob.			React.	Alb.	Glu.		
June, 1939	167	34	17				Van den Bergh immediate direct negative, delayed direct positive. Serum bilirubin 1.3					Trace of bile, no urobilinogen	Spinal and blood Wassermann negative. Colloidal gold negative. Creatinine 1.3

TABLE III

Blood Picture at Welfare Hospital

Date	Hgb.	R.B.C.	W.B.C.	Myelo-blasts	Myelo-cytes	Meta-myelo-cytes	Mature			Lymph.	Mono.	Miscellaneous	Remarks
							N	E	B				
Nov. 16, 1939	31%	1,940,000	8,200	1 pro. 1	2	19	37	3	0	34	3	Volume index .94 Platelets 250,000 Retic. 1.4 Normoblasts 11 per 100 w.b.c. Anisocytosis Microcytosis Sed. rate 11.5 Wintrobe	Leukoerythroblastic anemia
Nov. 21, 1939												Clot retraction 2 hours	
Nov. 24, 1939	40%	1,680,000	10,250			23	48			29		Normoblasts 15 per 100 w.b.c. Achromia, aniso., poik., etc.	Fragility .55–.20 Bleeding time 3 min. Clotting time 6 min.
Dec. 1, 1939	42%	2,140,000	8,250			14	52			34		Color index 1.0 Prothrombin 10 min. Platelets 225,000 Retic. 1% Normoblasts 13 per 100 w.b.c.	
Jan. 10, 1940	35%	1,800,000	10,250	pro. 1	12	13	52	2		13	1	Normoblasts 2 per 100 w.b.c.	After transfusion
Jan. 27, 1940	22%	2,030,000	6,450	pro. 4	1	14	58			23		Normoblasts 5 per 100 w.b.c.	
Feb. 6, 1940	28%	1,240,000	5,600	pro. 1		10	58			30	1		
Mar. 1, 1940	21%	1,370,000	8,000			18	65			46	1	Color index .8 Platelets 110,000	

TABLE IV

Laboratory Data at Welfare Hospital

Date	Glu.	Blood Chemistry					Miscellaneous	S.G.	Urine			Microscopic and Other	Other Tests
		N.P.N.	Urea N	Total Prot.	Alb.	Glob.			React.	Alb.	Glu.		
Nov. 14, 1939								1010	acid	2+	neg.	Negative	
Nov. 16, 1939		32.8	13.5										Wassermann and Kline negative
Nov. 17, 1939													Stool-Benzidine positive
Nov. 20, 1939							Uric acid 4.4 Cholesterol 329.9						Icteric index 5. Wassermann and Kline negative. Van den Bergh negative direct
Nov. 21, 1939												Bile negative	
Nov. 27, 1939													Urine concentration: 5 a.m. 220–1010 7 a.m. 215–1009
Nov. 29, 1939				7.14	4.46	2.68	Cholesterol 265.5						
Dec. 5, 1939							Cholesterol 268.0 Cholesterol esters 182.5 mg.						
Jan. 8, 1940	116		10.5				Phosphatase 7.29 B.U.						
Jan. 15, 1940				5.95	4.26	1.69	Ca. 8.6 Ph. 3.9						

section it was yellow-brown. Many pale yellow specks, 1.5 mm. in diameter, were noted, as well as many small petechial hemorrhages. Portal circulation was normal. Intrinsic and extrinsic biliary system was normal.

Gall-bladder was normal.

The pancreas weighed 150 grams. It was firm and lobulated.

Genitourinary tract: The left kidney weighed 170 grams, the right kidney 300. The capsule stripped easily. There were a few sparse, flat, irregular, depressed scars on surface. The cortex and medulla were sharply demarcated. Both pelves were slightly dilated. Both ureters were patent, and the right was dilated.

Bladder, prostate, adrenals, and thyroid were normal.

The parathyroids were not found.

Lymph nodes: Cervical, peritracheal, peripancreatic, aortic and retroperitoneal nodes were found to be enlarged. Some were discrete, others matted. Most were pale white and of rubbery consistency. Some were reddish brown.

FIG. 1. Illustrating thickness and sclerosis of calvarium.

Skeletal: Calvarium (figure 1) was 1 cm. thick. The cortical bone was homogeneous, the marrow space absent and the quantity of red marrow slight. Ribs and sternum showed increased thickness, were dense and hard throughout. Marrow cavity was diminished in size; the marrow was red and scant. The vertebrae showed marked bony sclerosis, were hard and dense; the marrow was scant. In the left femur (figure 2) only a thin marrow channel was present in the middle third. It contained a small amount of reddish yellow gelatinous marrow in the midst of bony trabeculation. The diameter of this cavity was 1 cm. The remainder of bone, including both ends, was dense and sclerotic with dense rim of bone on surface.

Histological:

The spleen (figure 3) had been removed in 1935. A review of the slide showed the capsule to be thickened. The architecture of the spleen was distorted by an increased cellularity and apparent thickening of the cords of Billroth. The lymph

follicles were diminished in size and quantity. A few small hemorrhagic foci were seen. There was hemosiderosis in areas. The outstanding feature of the section was the presence of many multinucleated giant cells. These were of more than one variety. They varied in size from 15.0 to 32.2 mu. Their shape was irregular; the cytoplasm was eosinophilic; some contained hemosiderin. The nuclei were vesicular, polymorphous and monstrous in shape. They were arranged in heaped up clusters in the

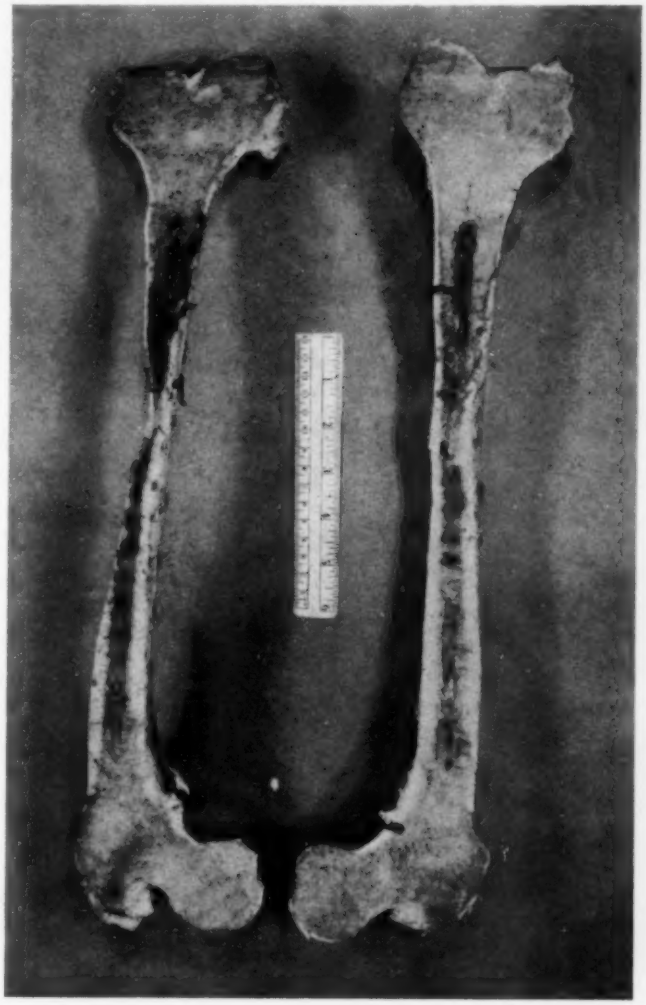

FIG. 2. Illustrating sclerosis of femur and diminution of marrow cavity.

centers of some cells, and peripherally in others. The remainder of the cells comprising the parenchyma consisted largely of myeloid cells with some reticulum cells and lymphocyte-like cells. There were also a few small islets of erythropoiesis seen.

Skin biopsy: Stain for iron negative.

Adrenal: The loose periadrenal fat tissue contained many cells of myeloid and lymphoid type. There were also plasma cells, histiocytes and monster giant cells re-

sembling those seen in the spleen except that they were smaller and their nuclei had a tendency to be hyperchromatic.

Skeletal: Skull: Marked thickening and an increase in the number of bony trabeculae were found. Marrow spaces were small and contained scant loose and matted elongated marrow cells and fibroblasts. Hematopoietic cells were scant; some lymphocyte-like cells were present. Rib: distinction between cortex and medullary space was lost. Both layers were similar and contained many irregular thickened bony trabeculae. The marrow spaces were small and distorted. Their contents

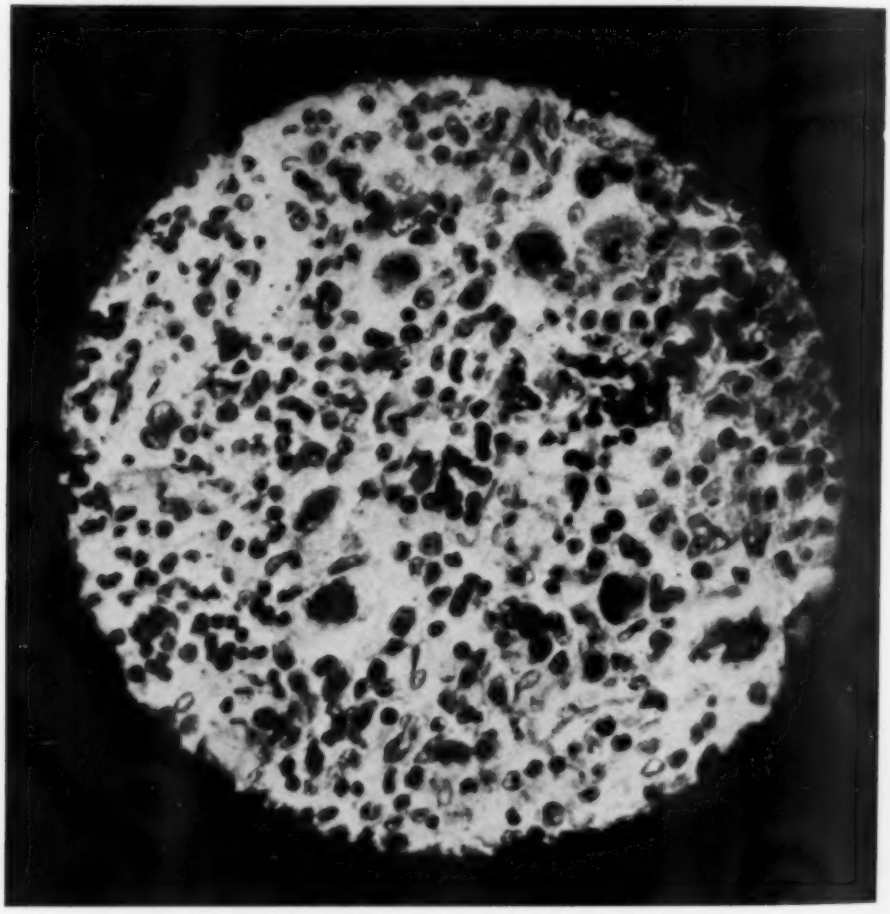

FIG. 3. Giant cells in spleen. Magnification 313.5 ×.

were loosely cellular and variable. Some spaces contained elongated marrow cells. There were a small number of multinucleated giant cells with hyperchromatic nuclei and scant cytoplasm. These cells resembled those seen in the spleen but were smaller. The remainder of the cells were myeloid, erythroid and lymphocyte-like. Moderate hematopoiesis was found; metamyelocytes and polymorphonuclears were scant. Many normoblasts were seen. Vertebrae: structure was similar to that of rib. Multinucleated giant cells were present in larger numbers; matting of elongated marrow cells was more prominent; there were many normoblasts.

Femur (figure 4): upper end of shaft resembled section from rib and vertebrae. Minor differences were: fewer giant cells, less cellularity of marrow spaces, more prominence of fat in some of the spaces. A few small islets of dense cellular collections similar in appearance to the type of cells above described were found. Bony trabeculae were irregular, conspicuous, thicker and quantitatively increased.

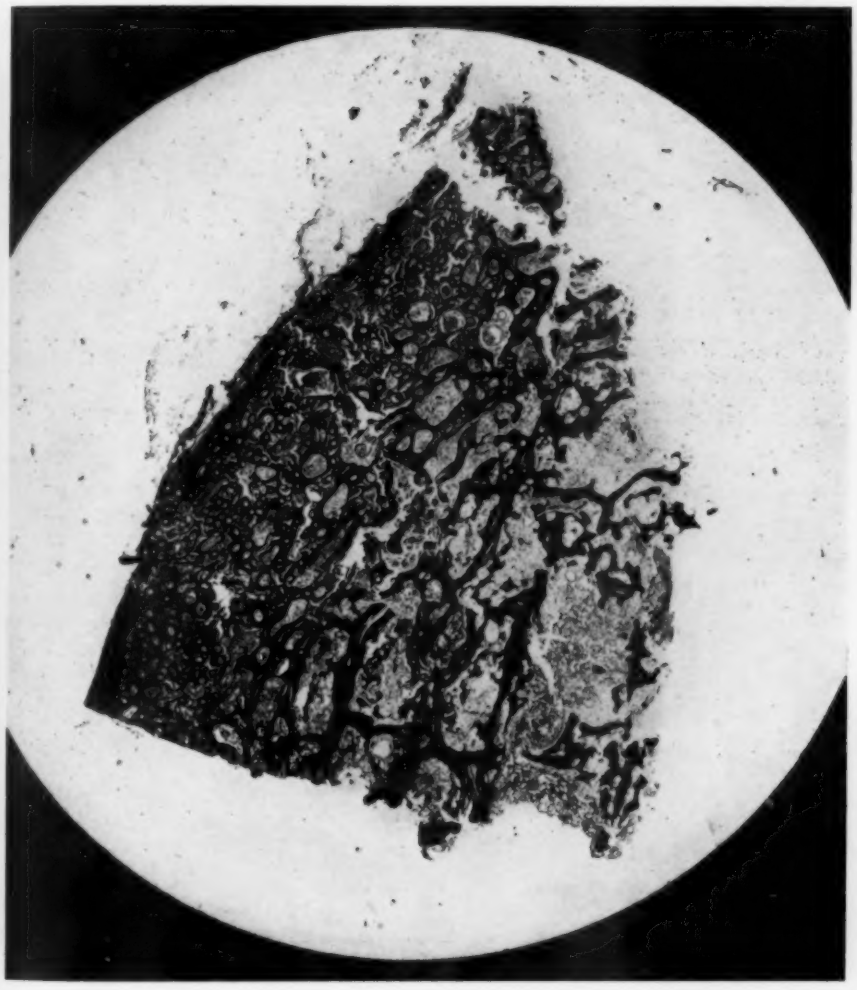

FIG. 4. Section of femur from periphery illustrating sclerosis. Magnification 6 ×.

(Figure 5): Marrow scooped out from shaft: sections disclosed an increased cellularity invading a moderately fatty marrow. The architecture was normal but there was a preponderance of erythroid over the myeloid cells. Very few mature hematopoietic cells were seen. In some regions there was matting of the marrow cells. Some giant cells were found.

Aorta: Moderate atheroma.

Heart: Myocardium showed hypertrophy of the muscle fibers as well as marked degenerative changes. There was much separation of fibers due to edema in some

areas, and to fibrosis in others. The papillary muscles showed large areas of fibrosis as well as groups of lymphocytes and histiocytes apparently in response to myocardial degeneration.

Valves: The vegetations appeared to consist of amorphous acellular material which stained both eosinophilic and basophilic. No bacteria were found.

Kidneys: A moderate degree of degeneration of tubular epithelium was present.

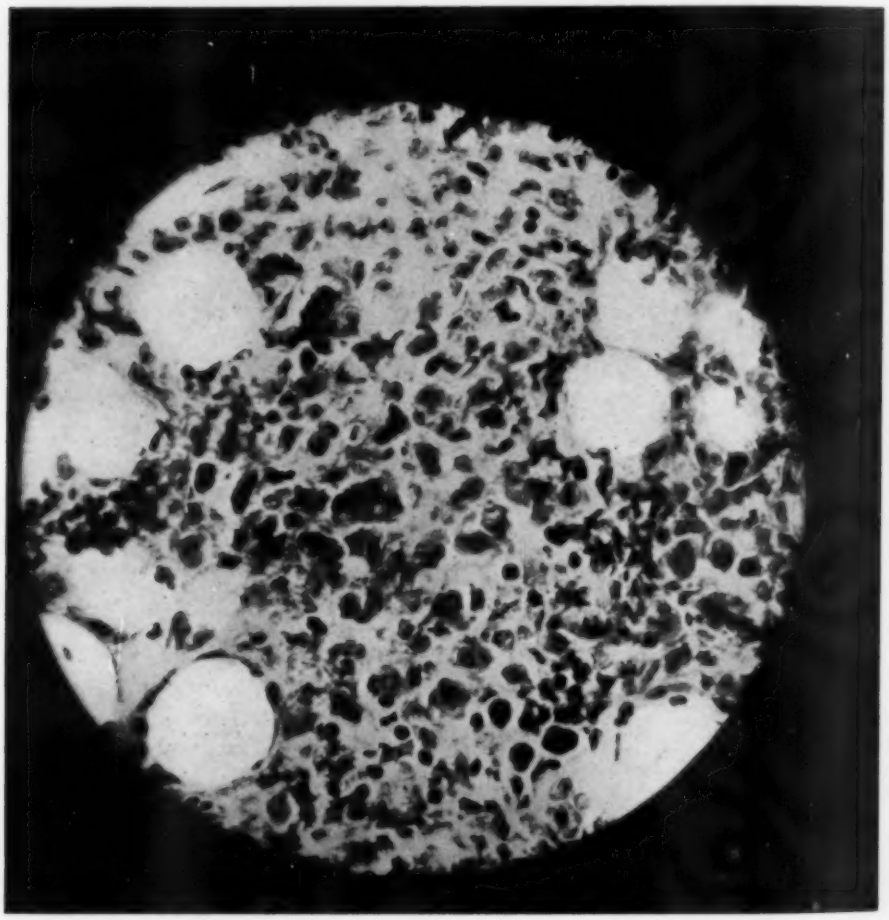

FIG. 5. Section of marrow scooped out of femur illustrating giant cells and cellular content. Magnification 110 ×.

No fat or anisotropic material was found in them. The glomeruli were well preserved. Only a rare sclerotic arteriole was seen. The medulla showed a slight degree of round cell infiltration.

In the liver numerous small areas of hemorrhagic necrosis were present. Parenchymal cells were shrunken and degenerated. Many contained large quantities of brown pigment which gave the blue reaction for iron. There was a marked increase of fibrous tissue about the portal spaces and between the lobules. Numerous small foci of lymphocytes were seen, particularly in relation to the areas of fibrosis. Some fatty degeneration was present. Rare islets of hematopoiesis were seen.

Lymph nodes (figure 6) (Cervical, mediastinal, bronchial, perigastric, periaortic and retroperitoneal); The histological changes of the enlarged lymph nodes were essentially similar. The architecture was considerably distorted so that only an occasional follicle persisted. Those which were present did not have germinal centers. The contents of the nodes were partitioned by connective tissue trabeculae. The most common cell present was the small lymphocyte. The outstanding abnormal feature

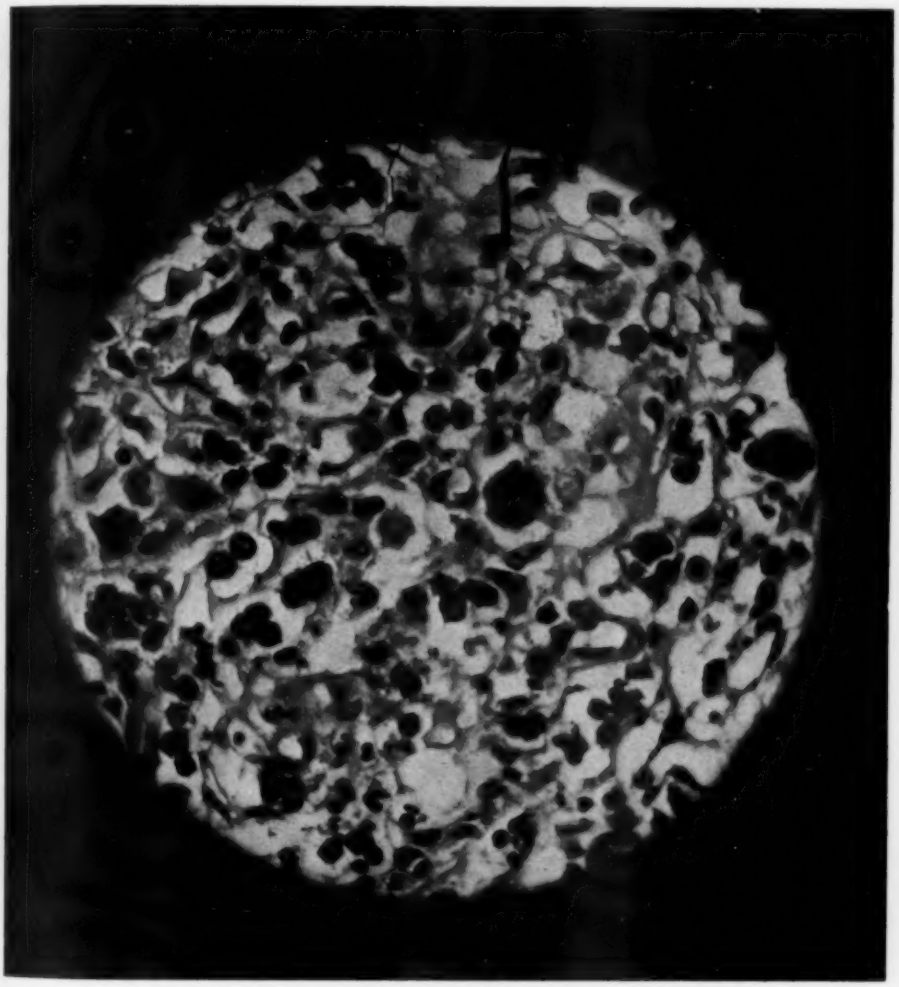

FIG. 6. Typical lymph node illustrating giant cells and architectural disorganization. Magnification 313.5 ×.

was the presence of numerous polymorphous giant cells. These were of several varieties. There were some which were mononuclear, the nucleus being monstrous, intensely basophilic in some cells and vesicular in others. The cytoplasm was distinct and usually eosinophilic. The shape of the cell was irregular. Some of these cells showed phagocytosis of erythrocytes and small lymphocytes. Other giant cells were multinuclear. Of this variety some contained many heaped up vesicular oval nuclei in

their centers; others, which were less frequent, disclosed a peripheral arrangement of nuclei. There was marked variation in the size of all the giant cells. The lymph nodes also contained many phagocytes and histiocytes. The former were loaded with a fine brown pigment which gave a blue stain for iron. Capillaries and sinuses were distinct and thin walled. The blood vessels showed no abnormalities. Scant hematopoiesis was present. The several varieties of giant cells were more numerous in the small and medium sized lymph nodes than in the large ones. The perilymphatic adipose tissue contained a moderate lymphocytic infiltrate.

Lung: There was moderate atelectasis with collapse of the alveoli. The capillaries in the walls were engorged with erythrocytes. Occasional heart failure cells were present in the alveoli.

Pancreas: The parenchymal cells contained a moderate amount of brown pigment which appeared blue when stained for iron. The cells at the periphery of the lobules appeared atrophied.

Pituitary: There were no marked abnormalities.

Histological Diagnosis: *Blood:* Leukoerythroblastic anemia. *Liver:* Hepatomegaly, cirrhosis, hemosiderosis, hemorrhagic necrosis, extramedullary hematopoiesis. *Skeletal:* Osteosclerosis—diffuse; giant cell hyperplasia. *Lymph Nodes:* Giant cell hyperplasia, hemosiderosis, extramedullary hematopoiesis. *Heart:* Hypertrophy; myocardial degeneration and fibrosis; terminal endocarditis, mitral and aortic valves; pericardial effusion. *Lungs:* Pulmonary edema, atelectasis, congestion, hydrothorax, bilateral. *Pancreas:* Hemosiderosis. *Additional:* Hydrocele, ascites, general anasarca. *Spleen:* Splenomegaly (splenectomy), multiple infarcts, giant cell hyperplasia, myeloid hyperplasia, hemosiderosis, extramedullary hematopoiesis.

Discussion

An examination of the literature for cases of leukoerythroblastic anemia and osteosclerosis reveals that these symptom complexes may occur either alone or together. Furthermore, they may either be associated with other disease complexes or may occur without relationship to any other known disease. The entire situation is complicated by the unknown etiology of most of these various states.

In the differential diagnoses for osteosclerosis, the following diseases must be considered:

Albers-Schoenberg disease presents itself as an outstanding condition characterized by diffuse osteosclerosis. However, not all the cases show hematological disturbances. Some are reported associated with moderate to severe anemia, others contain descriptions of leukoerythroblastic anemia and still others have no anemia. The disease occurs in a young age group, and a history of consanguinity is occasionally present. The etiology is entirely obscure. Where both occur, it has not been possible to establish the precedence of either osseous or hematologic change.

Cases of Hodgkin's disease of the skeletal system exclusive of lymph node involvement have been reported only by E. B. Krumbhaar and another by S. K. Livingston, the former case having an anemia, whereas in the latter the blood picture was normal. However, roentgenographic changes of the bones in Livingston's case were described as rarefaction and osteolysis, resembling metastatic neoplastic disease. In our case, the bone lesions were diffuse rather than infiltrative, there being no single bone focus that could be described as discrete.

Generalized osteosclerosis has been described in cases of chronic fluorine intoxication among workers in a Copenhagen cryolite factory. The cases are too few to warrant a definite conclusion.

The association of osteosclerosis with various blood dyscrasias is more complex. The following disease states have been reported to be associated with such bony changes: chronic myelogenous leukemia, chronic lymphatic leukemia, multiple myeloma, polycythemia vera, and aplastic anemia. J. M. Vaughn and C. O. Harrison describe a case of a female 43 years of age who had had polycythemia in the past and splenomegaly of seven years' duration. Her polycythemia was followed by a leukoerythroblastic anemia and at autopsy osteosclerosis was found to be present.

The situation as regards aplastic anemia associated with osteosclerosis has been analyzed by C. P. Rhoads and D. K. Miller. In an analysis of idiopathic progressive anemia (not responding to any known hemopoietic agents) they distinguished five subgroups from histological examination of the bone marrow: (1) aplastic anemia with aplastic marrow; (2) aplastic anemia with hyperplastic marrow; (3) aplastic anemia with active marrow; (4) aplastic megakaryocytic marrow; (5) aplastic anemia with sclerotic marrow. More recently C. P. Rhoads has substituted the name of primary refractory anemia for aplastic anemia. He also points out that the various subgroups cannot be sharply defined, some cases being intermediate, and that marrow biopsy revealed one type whereas autopsy on the same case revealed another type of pathologic lesion. He urges that too much significance should not be placed on the classification into independent types.

According to this classification, our case, although not one of aplastic anemia and not strictly fitting into any one of the subdivisions, could simply be considered as one of refractory anemia with osteosclerosis.

Comment

The disease occurred in a male 50 years of age, ran a continuous progressive course for seven years and did not respond to splenectomy, liver or iron therapy. Ninety-five transfusions which were given during his illness appeared only to prolong life but had no effect on the disease. During the fifth year of his illness, he experienced a severe hemorrhage following the removal of a loose tooth. Three months later he had spontaneous hemorrhages from the gums. With present means of study, it is apparent that the hematological changes preceded the bone changes, since early skeletal roentgenographic examinations were negative and osteosclerosis was only discovered during his last hospital admission.

The peripheral blood changes were characterized by a severe normochromic normocytic anemia. Color index varied between 1.0, 0.9 and 0.8. Volume index was reported as .94 and mean corpuscular volume as 90. On two occasions the leukocytes (early in the course of the disease) were reported at 44,810 and 80,000. Subsequently they varied between 13,300 and 5,600, reaching the lower levels in the late stages of the disease. A leukoerythroblastic peripheral blood smear was consistently present. Terminally the platelets were 110,000. No abnormal platelets were seen.

The presence of a leukoerythroblastic picture is interesting. A case manifesting this feature was recently described by Carpenter-Flory. The authors also present an excellent summary of the literature.

Whether this was a compensatory mechanism because of the marked osteosclerosis and myelofibrosis, or whether this was a cardinal feature of the disease is unknown. Unfortunately, there are no detailed blood studies during the early periods of this disease. The enlargement of numerous lymph nodes and the accumulation in them of megakaryocytes implies the participation of these glands in the disease. The accumulation of pigment is probably secondary to the repeated transfusions. None of the glands presented the picture of leukemia.

As stated, the etiology of this condition is entirely uncertain. We believe that it would perhaps be best to follow the criteria described by C. P. Rhoads for hematological disturbances of this type and to consider it a case of idiopathic progressive refractory anemia.

Conclusion

The case presented was one of chronic progressive leukoerythroblastic anemia, unresponsive to any form of treatment including splenectomy, and associated in the later stages with osteosclerosis. Pathologically, the outstanding features were leukoerythroblastic anemia, cardiac hypertrophy, myocardial fibrosis, extensive giant cell accumulation in the spleen, bone marrow and lymph nodes, and extensive osteosclerosis.

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INSULIN RESISTANCE (WITH OBSERVATIONS IN AN UNUSUAL CASE) *

By JACOB J. SCHLOSS,† M.D., *Boston, Massachusetts*

A CASUAL reader of the literature on diabetes may get the impression that "insulin resistance" is of rather frequent occurrence. A more careful study, however, makes it obvious that various authors refer to different phenomena when speaking of insulin resistance.

Falta and his pupils [16, 17, 19] attempted to classify diabetics into the two groups of "insulin sensitive" and "insulin resistant" cases. This classification was based on the results of special methods for determining the quantitative relation of insulin and carbohydrates. Recent statistics from Falta's clinic [20] demonstrate some parallelism between certain constitutional and clinical features and the more or less marked effect of insulin on hyperglycemia, glycosuria, etc. Cases of "insulin resistance" as defined by Falta comprise two different types: first, cases with increased insulin tolerance, and second, cases with increased insulin requirement. The latter expression is about synonymous with "decreased carbohydrate equivalent of the insulin unit." It does not seem advisable, in my opinion, to consider the carbohydrate equivalent of insulin, i.e., the amount of carbohydrate which one unit of insulin can help metabolize, the chief criterion in the classification of diabetics. It has been realized for many years that the carbohydrate equivalent is not at all a mathematical constant. It depends on numerous factors not all of which are controlled or even known. It is not surprising, therefore, that more than half of the cases reported by Fenz [20] from Falta's clinic could not be classified according to Falta's ideas. The carbohydrate equivalent may be helpful, in connection with other observations, in describing the condition of a diabetic patient at any given time. We have so used it in this paper. Moderate deviation from the usual figures as demonstrated by Falta's special tests should not be used to define insulin resistance and insulin sensitivity. If we are to follow Falta's suggestions at all, one should speak of cases with (1) slightly or moderately decreased carbohydrate equivalent, or (2) increased insulin tolerance, in order to avoid confusion with the type of patients to be discussed below.

We suggest reserving the expression "insulin resistance" for conditions which require the administration of several hundred, sometimes a thousand or more, units of insulin per day. Under these circumstances, the carbohydrate equivalent drops to less than 0.5, sometimes to less than 0.1 gram. It seems likely that absolute ineffectiveness of insulin, in the sense that insulin has not even the slightest effect, does not occur. Insulin resistance frequently develops in cases which previously showed a normal response to insulin. Occasionally patients return to the stage of normal insulin response after a period of insulin resistance.

Conditions that are recognized as factors in the causation of insulin resistance may be classified as follows:

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† Deceased.

1. Severe acidosis and diabetic coma: A large number of cases while in diabetic coma temporarily present the picture of relative insulin resistance according to the above definition. A few comatose cases have been reported in which unusually large doses of insulin failed to exert any appreciable effect (Thannhauser and Fuld [44]; Adlersberg and Porges [1]). They seemingly represented cases of absolute insulin resistance. Recent experience makes it doubtful whether this failure should be attributed to the ineffectiveness of insulin. Observations made by Falta [18] and by Root and Riseman [41] suggest that the expected insulin effect can be restored when doses of fluids and salts are given which far exceed those usually effective in the treatment of diabetic coma.

2. Infections: It is a common experience that infections frequently necessitate an increase in the dose of insulin and that with the drop of temperature and the disappearance of the other signs of infection the amount of insulin can be reduced to that used before the onset of the complication. Chronic infectious diseases occasionally require unusually large doses of insulin over a considerable period of time. Mohler and Goldburgh,[37] e.g., gave a patient with tuberculosis and other complications 16,515 units in 40 days. The maximum 24-hour dose of insulin in this case was 1150 units to metabolize 92 gm. of carbohydrate (corresponding to a carbohydrate equivalent of 0.08 gm.). Other remarkable cases in which infections were thought to be responsible for the development of insulin resistance have been reported by Depisch and Hasenoehrl [14] and by Byworth.[10] The observations of Wayburn [47] on a tuberculous diabetic deserve to be mentioned also. In spite of the administration of 415 units in 24 hours, this patient excreted as much as 122 gm. sugar. Therefore, it was assumed that insulin was more or less without effect and the dose was reduced to 70 units a day. This, however, was followed by coma and death. Once more the question arises as to how much the breakdown of the water and electrolyte metabolism and the anorexia in diabetics with fever may hamper the effectiveness of insulin. It is quite possible that the "insulin resistance" in many of these cases could be obviated by a treatment which aims to restore normal electrolyte, fluid and carbohydrate balances.

3. Diseases of the endocrine glands other than the pancreas: Reduced effectiveness of insulin may be expected when hyperglycemia and glycosuria are primarily due to diseases of endocrine glands other than the pancreas. This is known to occur in hyperthyroidism, in acromegaly and in pituitary basophilism.[13] Nevertheless, reports of instances in which very large doses of insulin were used with little or no effect are surprisingly scarce. On the contrary, Yater [50] found in six cases of acromegaly and diabetes studied at the Mayo Clinic that "the response to insulin was just as striking as in any cases of diabetes." Speaking of the inhibition of insulin action, Ulrich [45] pointed out that "there are gradations of antagonism in different patients with hyperpituitary disease, ranging from none at all . . . to almost complete inhibition . . ." and supports the latter statement with observations of his own. A patient of Hills, Sharpe and Gay [26] required increasing doses of insulin up to 890 units in 24 hours following thyroidectomy. However, several other complications in this case make it difficult to judge whether the change in the thyroid condition can be held solely responsible for the development of the insulin resistance. Altschuler and Gould [6] reported a case refractory to insulin in which the autopsy revealed a

large suprasellar cystic hematoma compressing the hypothalamic structures, including the anterior and posterior lobes of the hypophysis. Unfortunately the clinical observations are not quite conclusive.

4. Diseases of pancreas and liver: In contradistinction to the last group, a few cases which, without reserve, may be called insulin resistant result from destructive processes of the pancreas and liver. Several instances of insulin resistance were observed in hemochromatosis. The case of Root,[39] in which the autopsy showed hemochromatosis, called for increasing amounts of insulin. Shortly before death 1680 units of insulin a day were given. The patient of Wood and Fitz-Hugh [49] revealed a blood sugar constantly in the vicinity of 200 mg. per 100 c.c. on a diet of 100 gm. carbohydrates and 175 units of insulin a day. Increasing the dose of insulin had little if any effect. The patient finally died from a ruptured duodenal ulcer. Autopsy disclosed the typical findings of hemochromatosis. In another case of hemochromatosis verified by autopsy, Allan and Constam [3] gave up to 500 units of insulin a day. This type of response seems to be the exception. Most cases of bronzed diabetes usually respond well to insulin. They occasionally show, as Althausen and Kerr [5] first described, even high sensitivity to insulin with a tendency to insulin reactions. In a case of "acute hepatitis" reported by Root,[40] 510 units were necessary to lower the blood sugar from 1,290 to 420 mg. per 100 c.c. within six hours.

It is difficult to decide where the observations of Mason [34] should be classified. The patient, during the last eight months of life, required from 200 to 400 units of insulin a day, and finally the administration of 2,075 units in 24 hours became necessary. The autopsy disclosed, besides a very small fibrotic pancreas containing advanced calcareous degeneration, a cyst in the ventral part of the midbrain.

It is doubtful whether the case of Pollack and Long [38] can be classified as truly insulin resistant. In this patient the injection of 540 units of insulin in 24 hours led to a severe hypoglycemic reaction. Autopsy revealed recent thrombotic occlusion of all branches of the celiac artery.

Increased insulin tolerance in cases of jaundice was noted by Boller and Ueberrack.[8] None of their cases showed true insulin resistance. Passive congestion of the liver may be one factor in the increased demand of insulin in cases of cardiac failure.

5. Pathological changes of the skin: It seems that at times certain skin manifestations interfere with the prompt action of insulin. Cases of insulin resistance due to allergic reactions are reported (Allan and Scherer,[4] Williams,[48] Foerster [21]). The most impressive among these cases is the one described and discussed by Rudy.[42] Coincidental with urticaria his patient needed 515 units of insulin with a carbohydrate intake of about 200 gm.

6. Insulin resistance without demonstrable cause: In several cases of insulin resistance no reason could be demonstrated. Marble [35] recently published his experiences with a patient whom he had followed for about three years and whose diabetes continues to be well controlled. Her insulin requirement varied from 240 to 675 units in 24 hours, protamine insulin forming considerable fractions of this dose at certain times. Complications noted in this case were severe rheumatoid arthritis, general glandular enlargement, slight to moderate

hepatomegaly and splenomegaly, and eosinophilia. Frequently quoted observations are those of Glassberg, Somogyi and Taussig.[22] They gave a patient 26,965 units in less than three months. The carbohydrate equivalents ranged from 0.3 to 0.7 gm. At times there were allergic reactions to insulin, but the insulin resistance continued through periods when no such reactions were noted. Karr, Scull and Petty [31] reported a case with allergic skin reactions and insulin resistance. On one occasion as many as 600 units of insulin were required. They also felt that in their patient both abnormalities were independent. Although it does not seem very likely, there may be still some doubt whether the allergic skin reactions were contributory to the development of insulin resistance in the two cases just cited. However, there is no mention of skin reactions in the patient of Clay and Lawrence.[11] In spite of the fact that insulin was given in increasing amounts up to 960 units per day, "no demonstrable insulin action took place" and the patient died. At autopsy none of the conditions which occasionally cause insulin resistance could be demonstrated.

This review of the literature refers only to outstanding cases of insulin resistance, and those which throw some light on the problem. I should like to add a report of another case which revealed several unusual features. This patient was under my observation in the Medical Clinic of the University of Leipzig, Germany, from June 1929 to April 1932 and was briefly presented before the Medical Society of Leipzig.[43]

Case Report

G. H., female, born July 26, 1912, was admitted to the Ward for Metabolic Diseases on four occasions.

First admission. In December 1928, following pharyngitis, she noticed fatigue, a feeling of heaviness in the extremities, polydipsia and polyuria. There was polyphagia of moderate degree, pruritus, diminution of vision and loss of weight (7.5 kg. in eight weeks). About six weeks previous to admission she had occasional pain in the upper abdomen and in the left side of the chest. About one week before admission she developed small furuncles of the neck and the back.

Past history and family history were not contributory. Catamenia had been regular since the age of 14 years, but there had been amenorrhea for the previous 12 weeks.

On physical examination the patient was a well developed, well nourished, almost robust female. Height 157 cm., weight on admission 56.7 kg., on discharge 58.5 kg. There was a slight acetonemic fetor to the breath. Both eyes showed incipient cataracts. Teeth were in good condition. Tonsils were small and cryptic. There were several hyperemic scars of recently healed furuncles on the back. The breasts were well developed. Chest, heart and lungs were without pathological findings. Pulse rate 80. Blood pressure was 120 mm. Hg systolic and 85 mm. diastolic. There was slight tenderness on light palpation in the right upper abdomen, but hepatic and splenic dullness were within normal limits. Genitalia were normally developed. There was erythema of the vulva. Scar of a healed furuncle on the left thigh. The neurological examination was entirely negative. Blood sedimentation rate was normal. Wassermann, Kahn and Sachs-Georgi tests were negative.

During the first 24 hours patient's carbohydrate (CHO) intake was 100 gm. with 20 units of insulin before breakfast and 20 units before supper. The urine contained 42 gm. of sugar in 24 hours. Ferric chloride and sodium nitroprusside tests were positive; fasting blood sugar 274 mg. per 100 c.c. Within the next 24 hours the

acetone bodies disappeared from the urine, and at the end of three days sugar was absent. Insulin could be reduced to 15 units before breakfast and 15 units before supper and the fasting blood sugar dropped to 155 mg. per cent. Gradually the CHO intake could be increased to 170 gm., and 10 days after admission the insulin requirement was 10 + 10 units. Eleven days after admission the patient developed fever with a peak of 102.8° F. The temperature became normal within 48 hours and the fever was unexplained. Finally insulin could be discontinued entirely and the patient was sugar free on a diet consisting of 200 gm. CHO, 60 gm. protein (P), and 170 gm. of fat (F), totalling about 2600 calories. The last fasting blood sugar determined was 173 mg. per cent and the daily urine volumes averaged between 2000 and 3000 c.c.

Second admission, April 13 to July 16, 1930. Weight on admission 55 kg., on discharge 68.4 kg. Following discharge from the hospital the patient felt fairly well until Christmas 1929, when she again began to develop polydipsia and polyuria with a feeling of fatigue and general weakness. In January 1930 she had a furuncle of the gluteal region, and required 30 units of insulin a day. This could be discontinued after a few weeks. During the night of April 10, the patient vomited repeatedly.

The only changes on physical examination were acutely inflamed tonsils, scattered moist râles over the right lung, and a large deep furuncle of the right gluteal region which was about 4 to 6 cm. in diameter and exuded thick yellow pus. The temperature was elevated for the first 12 hospital days, rising to 104° F. on the tenth day. Roentgenographic examination of the chest was negative. Hemoglobin was 95 per cent; red blood cells 4,700,000; white blood cells 18,600. Smears were not remarkable.

During the first 18 hours after admission all urine tests showed strongly positive reactions with ferric chloride and sodium nitroprusside. The total food intake was 76 gm. CHO, 5 gm. P, and 3 gm. F. The total amount of insulin was 125 units and the total sugar output was 71 gm. Fasting blood sugar was 265 mg. per cent.

The urine gradually became sugar free. Thirteen days after admission, i.e., the day the temperature returned to normal, the patient tolerated a diet consisting of 100 gm. CHO, 75 gm. P, and 65 gm. F with 35 + 20 + 25 + 10 = 90 units of insulin, at 6 and 11 a.m. and 5 and 9 p.m. respectively. There was slight pitting edema which disappeared with the reduction of the insulin dose.

Four weeks after admission the furuncle had healed. The urine was sugar free. The food intake amounted to 85 gm. CHO, 75 gm. P, and 110 gm. F. Insulin was given—30 units at 6 a.m. and 25 units at 6 p.m. Fasting blood sugar was 133 mg. per cent. On July 16 she was discharged on a diet of 80 gm. CHO, 70 gm. P, and 110 gm. F with 45 units of insulin in two injections. The fasting blood sugar on the day of discharge was 184 mg. per cent, hemoglobin 95 per cent, red blood count 4,700,000, and white blood count 7,300.

Third admission (*in coma*) September 19, 1930 to March 14, 1931. Weight four days after admission 61.7 kg., on discharge 74 kg. The patient claimed that she adhered to her diet and insulin dosage during the months that had intervened since her discharge. Regular urine examinations showed negative sugar tests most of the time.

On September 17 the patient complained of fatigue and felt feverish. On September 18 she developed pain in the left thigh, and the family physician found a large tender hyperemic area. This was treated with alcohol compresses for 24 hours. On September 19 an abscess of the described area was incised under ether anesthesia. In the afternoon of the same day she was drowsy and vomited several times. Late in the afternoon she became comatose.

On admission to the hospital she was unconscious, with an intense acetonemic odor, dry skin, soft eyeballs, Kussmaul respiration, etc. Temperature was 101.3° F.,

pulse 124, blood pressure 90 mm. Hg systolic and 60 mm. diastolic. White blood count 17,200. There was a purulent crater about 2 cm. in diameter and 0.5 cm. in depth on the left thigh. Urine examinations showed strongly positive tests with ferric chloride and sodium nitroprusside. The urine sugar concentrations ranged from 1.5 per cent to 5.3 per cent. The patient responded to the usual coma régime and was sugar free on the fourth day. On this day her diet consisted of 70 gm. CHO, 45 gm. P, and 60 gm. F. $30 + 20 + 20 = 70$ units of insulin were injected at 6 and 12 a.m. and 6 p.m. respectively. Fasting blood sugar was 353 mg. per cent. The fever gradually subsided and the dose of insulin finally could be reduced to 25 units before breakfast and 25 units before supper. In the latter part of October she experienced a rather severe tonsillitis. Following recovery she was never completely sugar free on an adequate CHO intake and doses of insulin from 40 to 50 units a day. Fasting blood sugar ranged from 187 to 320 mg. per cent.

Tonsillectomy was performed on December 1; the recovery was uneventful. On January 1, 1931 patient was on a diet of 60 gm. CHO, 80 gm. P, and 90 gm. F. The insulin dose was $40 + 15 + 40 = 95$ units. The sugar output amounted to 36 gm. and the fasting blood sugar was 317 mg. per cent. Her temperature was within normal limits. By the end of the month $55 + 10 + 5$ units of insulin were necessary to keep the urine almost sugar free on a diet of 75 gm. CHO, 90 gm. P and 70 gm. F. The fasting blood sugar averaged about 190 mg. per cent. Reduction of the CHO intake to 30 gm. in 24 hours without insulin was followed by aglycosuria and the fasting blood sugar fell to a normal level.

From January 28 until February 22, the temperature was elevated occasionally and at one time (February 4) reached 104.9° F. The source of the fever could not be discovered. On one occasion there was tenderness on pressure over the twelfth dorsal and first lumbar spinous processes. Roentgenographic examinations of the complete spinal column were negative. On two occasions a few leukocytes were found in catheterized specimens and urine cultures showed growth of enterococci. Specimens collected from both ureters separately, however, proved to be sterile and showed nothing but a few leukocytes. Urine cultures for tubercle bacilli and guinea pig inoculations were negative. Stool examinations did not disclose any abnormal findings. Flat plates of the abdomen, pyelograms, gastrointestinal series and roentgenographic examinations of the lungs did not suggest any pathological changes. Pelvic examination failed to reveal any findings that might be considered the cause of the fever.

Repeated basal metabolism determinations showed normal values. Roentgenographic examination of the skull and lumbar puncture did not suggest a lesion of the brain. During the last 10 days in the hospital the fasting blood sugar dropped from 241 to 169 mg. per cent. After being afebrile for more than two weeks the patient was discharged. At this time her diet consisted of 60 gm. CHO, 80 gm. P, and 80 gm. F. Even with $50 + 25 + 30 = 105$ units of insulin there was a trace of sugar in each specimen but the total amount of glucose within 24 hours never exceeded 2 gm.

Fourth admission. June 28, 1931 to April 10, 1932. Weight on admission, 61.4 kg., on discharge 64.6 kg. Following discharge from the hospital the family physician decreased the daily amount of insulin 95 units. Elevations of temperature were observed several times during the first two weeks at home. She was never entirely sugar free. Subjectively she felt so well that she was able to go back to work. On the day previous to the fourth admission while shopping she developed air hunger and vomited. She was unable to walk home and was brought to the hospital by ambulance.

On admission the temperature was found to be 101.8° F. Pulse was 124, and respiration of the Kussmaul type. There was a marked acetonemic fetor, ocular tension was normal and leukocytes 10,400. There was intense redness of the pharyn-

TABLE I

Observations Made at Time of Fourth Admission for 280 Days (Figures Represent Averages of 10 Day Periods)

Date	Insulin Urine Output				Weight kg.	Fasting Blood Sugar mg. per 100 c.c.	Intake				Notes
	Units	Number of Injections	Glucose grams	N ×6.25 grams			CHO gm.	Prot. gm.	Fat gm.	Calories	
7/ 1– 7/10	124.5	3.5	134.1		63.2	359	49	50	54	908	Elevated temperatures until July 2
7/11– 7/20	290.5	4.3	133.6		63.3	555	45	53	48	848	Subjectively improved; gets up for 1–2 hours
7/21– 7/30	160.0	1.5	194.0	54.7	63.6	646	42	71	42	854	General condition improved
7/31– 8/ 9	224.5	4.3	241.9	62.1	62.5	834	76	29	63	1016	Condition same
8/10– 8/19	469.0	13.6	258.2	77.0	63.7	610	100	52	59	1172	Laryngitis and bronchitis; elevated temperatures from Aug. 15 to 17. Highest temperature Aug. 16: 103.6° F.
8/20– 8/29	495.5	12.8	340.6	115.4	62.3	594	122	51	50	1174	Rise in temperature August 23–24; highest temperature 101.8° F. Bed rest
8/30– 9/ 8	353.0	11.9	256.3	79.7	65.1	486	91	44	43	953	Feels better; bed rest
9/ 9– 9/18	295.5	9.8	297.8	104.9	63.7	406	73	37	50	916	Occasional elevated temperatures; bed rest
9/19– 9/28	366.0	10.1	294.8	82.3	63.5	415	109	84	60	1349	Gets up. Fatigue and weakness
9/29–10/ 8	397.0	14.0	104.0	91.5	59.8	345*	55	37	90	1214	10/1 to 10/5: Catamenia. General ill feeling. Tachycardia, cyanosis, loss of appetite; furuncle of both labia majora. 10/6—temperature 102.5° F., and W.B.C. 11,000
10/ 9–10/18	600.0	17.0	92.3	100.1		345*	41	56	116	1476	Furuncle of left labium majus. Fever maximum 10/17, 105.2° F. W.B.C. 9,600
10/19–10/28	226.0	6.2	47.8	48.6		130	50	66	130	1684	Furuncles in both gluteal regions. Temperature elevation to 102.7° F.

TABLE I—(*Continued*)

Insulin Urine Output							Intake				Notes
Date	Units	Number of Injections	Glucose grams	N ×6.25 grams	Weight kg.	Fasting Blood Sugar mg. per 100 c.c.	CHO gm.	Prot. gm.	Fat gm.	Calories	
10/29–11/ 7	210.0	6.0	58.7	54.6	62.6	145	57	73	144	1872	Furuncles healed. Temperature normal. Generally improved. Sits up
11/ 8–11/17	266.0	9.8	14.8	48.3	64.1	260	56	71	146	1878	Improved
11/18–11/27	228.0	8.7	66.5	61.0	64.7	376	52	74	139	1809	Feels fairly well
11/28–12/ 7	407.0	14.1	134.7	62.5	64.4	438*	46	64	120	1567	Furuncle left thigh. Continuous high temperatures since December 1
12/ 8–12/17	495.0	17.1	146.4	64.0	65.2	340*	43	64	123	1582	Furuncle. Temperatures still elevated
12/18–12/27	540.0	18.3	157.9	50.7	66.3	331*	52	69	131	1714	Furuncle healed; temperatures normal. Feels fairly well
12/28– 1/ 6	463.0	17.0	192.9	71.2	65.7	423*	55	78	138	1828	Complaining of general weakness
1/ 7– 1/16	473.5	15.2	114.7	59.2	65.1	332*	81	64	106	1580	1/12—Comatose for a few hours; 50 units of insulin intravenously. Menstruation 1/11–12
1/17– 1/26	438.5	14.2	105.3	72.3	62.1	289*	87	65	107	1618	1/25—Comatose; 100 units of insulin intravenously
1/27– 2/ 5	358.0	8.2	50.0	51.3	62.9	479	150	83	47	1392	Improved on diet comparatively high in CHO
2/ 6– 2/15	400.0	8.8	73.4	23.4	61.9	493	140	89	64	1534	Complains of tiredness and weakness. Objectively rather alert
2/16– 2/25	536.0	10.4	145.1	47.0	62.2	299	170	72	35	1358	Furuncle left upper leg. Fever since 2/22
2/26– 3/ 6	656.0	11.7	171.7	59.3	59.6	488	159	86	43	1404	Fever continues until 2/29
3/ 7– 3/16	1079.0	12.6	170.9	76.0	56.8	310	155	53	27	1103	Catamenia March 13–17; no fever
3/17– 3/26	970.0	11.7	129.7	65.4	55.0	433	82	58	123	1717	Feeling comparatively well. Furuncles healed; no fever
3/27– 4/ 5	970.0	10.9	104.9	52.3	54.7	323	134	82	102	1834	Urine contains leukocytes, rare hyaline casts and epithelial cells. No fever

* Indicates that the fasting blood sugar was taken less than five hours after the injection of insulin.

geal mucosa, and of the vocal cords. There were numerous rather coarse râles over both lower lobes of the lungs. The liver was palpable, firm and slightly tender. Splenic dullness was within normal limits. There was tenderness on pressure over the deep muscles of the back. Treatment for impending coma was immediately instituted. During the following three or four days it was recognized that very large doses of insulin were almost or entirely ineffective.

Table 1 summarizes observations made from July 1, 1931 until April 5, 1932. In order to save space and to enhance the clearness, the figures are given in averages of 10 day periods. For instance, the grams of glucose excreted during 10 succeeding days have been totaled and then divided by 10, etc. This obscures certain details, but significant ones will be considered later. The table does not include the first three days since they were devoted to the treatment of the impending coma and to attempts to institute a maintenance diet and a maintenance dose of insulin. The last five days of the hospital stay were given to special studies and, therefore, are omitted.

The glucose concentration in the urine was determined with the polarimeter after removal of the β oxybutyric acid. Blood sugar examinations were carried out with the micro-method of Hagedorn and Jensen.[23, 24] The original method using 0.1 c.c. of blood does not permit accurate estimations of blood sugar concentrations as encountered in this case. Therefore, the determinations were made on 0.02 and 0.05 c.c. of blood, in order to bring the final concentrations within the range of the method. Carefully calibrated pipettes were used. Numerous blood sugar curves, many of them over a period of 24 hours, were taken to determine the further course of treatment. They could not be included in this paper. Nitrogen analyses were made by the macro-Kjeldahl method and their results were expressed in terms of protein ($N \times 6.25$).

Much care had been taken to obtain accurate CHO, N, water and salt balances. In the beginning these studies seemed to indicate that the generally assumed but not proved fact of CHO formation from fat could be demonstrated in this case. It was finally discovered that the patient obtained food from relatives and possibly from other patients, which unfortunately nullified our endeavors in this direction. In spite of her denials it is quite possible that she received considerable amounts of unaccounted nourishment. Therefore, the figures given for the intake in table 1 have to be considered as food orders and are at times possibly considerably smaller than the actual intake.

Further details can be seen in table 1. It shows among other things the unusually large amounts of insulin necessary to keep this patient fairly comfortable for almost 10 months, with the exception of periods when she developed furuncles or almost fell into coma.

The patient left the hospital against medical advice. It was suggested to the family physician that 600 units of insulin be given in seven injections daily, and that their effect be checked by frequent urine examinations. The patient died at her home in diabetic coma 12 days after her discharge from the hospital. Autopsy was refused.

Discussion

The patient was under our observation for a period of 22 months, 17½ of which were spent in the hospital. Table 2 summarizes briefly the course of the disease.

After the admission in June 1929 she reacted to diet and insulin like any mild juvenile diabetic. During the following admissions the amount of carbohydrate tolerated decreased, and the dose of insulin required to render the urine sugar free increased. On the fourth admission, there seemed to be no response at all to insulin. Finally it was discovered that when using excessively large doses of

TABLE II

Data Observed on Admission and on Discharge During the Four Periods of Hospitalization

No. of Admission	Condition on Admission	Observations One Day After Admission					Observations One Day Before Discharge				
		CHO Intake gm.	Glycosuria gm.	Insulin units	CHO Equivalent gm. per unit	Fasting B.S. mg. per 100 c.c.	CHO Intake gm.	Glycosuria gm.	Insulin units	CHO Equivalent gm. per unit	Fasting B.S. mg. per 100 c.c.
1.	Mild acidosis	103	42	40	1.53	274	200	0	0	—	173
2.	Severe acidosis	111	7	60	1.73	265	74	0	45	1.65	184
3.	Coma	76	38	70	0.54	353	52	1	100	0.51	169
4.	Impending coma	74	134	80	?0	331	132	38	1000	0.09	(94*)

* B.S. 2 hours after injection of 100 units of insulin while fasting.

insulin a fraction of the ingested carbohydrate was metabolized. In spite of the very liberal use of insulin there was only one day when the urine remained sugar free for an entire 24 hour period. Studying table 1 we arrive at a few amazing figures. During 280 days the patient received 124,915 units of various brands of insulin in 3037 injections. The sugar output in the urine amounted to 42,330 gm. (about 93 lbs.). The average insulin dose in 24 hours was 446 units, and the average number of injections 10.8. The highest fasting blood sugar was 892 mg. per cent; on this day the patient felt well. The maximal glycosuria with insulin (375 units in 10 injections) on a single day was 489.2 gm., and without insulin 535.8 gm. The maximal dose of insulin in a 24 hour period was 1630 units given in 17 injections.

It has been intimated above that a slight effect on hyperglycemia and glycosuria was obtained with very large doses of insulin. This cannot be recognized from table 1 because it was impossible to maintain the same type of treatment over a period of 10 days, or to omit insulin for such a period without endangering the patient. However observations over several days showed repeatedly that insulin had some effect although much less than might have been expected. On a constant diet the glycosuria followed roughly the dosage of insulin as shown in tables 3 and 4.

Figure 1 demonstrates similar relationships between blood sugar and insulin. In this diagram two blood sugar curves are compared, one without insulin, the other after a single injection of 500 units. The patient was fasting during the

TABLE III

Food Intake: CHO 49 gm.; P 67 gm.; F 55–65 gm.

Date	Time of Insulin Injections	Doses Units	Total Insulin Units	Glycosuria gm.
July 20	6 a.m.; 12 noon; 7 p.m.	100+50+50	200	122.2
July 21	No insulin	0	0	224.5
July 22	6 a.m.	150	150	141.7
July 23	No insulin	0	0	223.1
July 24	9 a.m.; 6 p.m.	100+100	200	123.9

TABLE IV

Food Intake: CHO 55 gm.; P 75 gm.; F 135 gm.

Date	Time of Insulin Injections	Doses Units	Total Insulin Units	Glycosuria gm.
Jan. 3	4, 6, 7, 8 9, 10, 11, 12 a.m. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 p.m.	50, 100, 20, 20 20, 20, 20, 50 20, 20, 20, 20 20, 20, 20, 20 20, 20, 20	520	159.5
Jan. 4	No insulin		0	475.2
Jan. 5	Same as Jan. 3. minus 50 units at 4 a.m.		470	215.1
Jan. 6	Same as Jan. 3	Same as Jan. 3	520	154.0

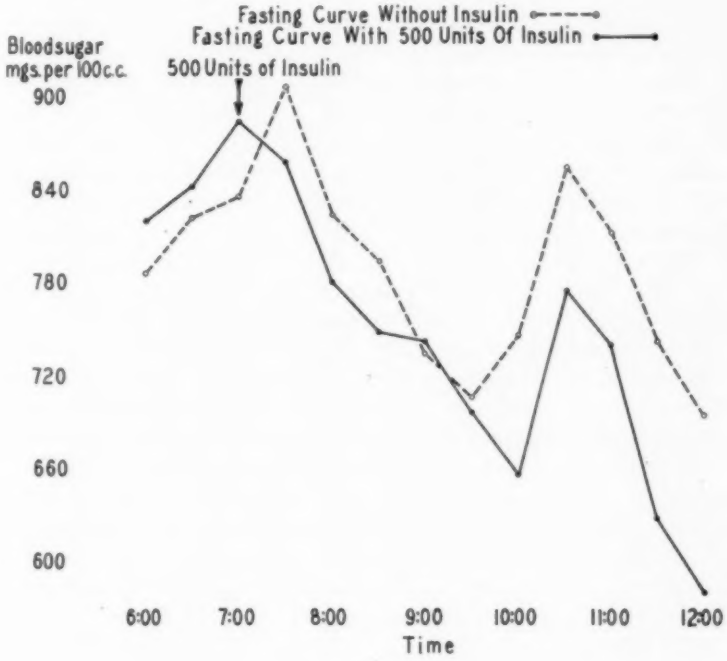

FIG. 1.

two experiments. The fasting blood sugar curve with insulin although starting from a slightly higher level runs below the fasting blood sugar curve without insulin. This difference is greater than the probable error.

These observations as well as the quoted reports from the literature, cast doubt upon the existence of absolute insulin resistance. Several unsuccessfully treated cases of insulin resistance justify the impression that increase of the already exceptionally high dose of insulin may have prevented coma and death.

There remains the question: "What was the cause of the remarkable insulin resistance in the case under discussion?" No definite explanation can be offered. There was no reason to assume greater involvement of the endocrine

glands than in other severe cases of diabetes mellitus. To be more specific, there were no signs of a macroscopic tumor of the pituitary or adrenal glands on roentgenographic examination. There were no clinical findings suggesting acromegaly or Cushing's syndrome. The basal metabolic rate was within normal limits. The menstrual disturbances did not exceed those frequently observed in poorly controlled diabetics.

The liver was palpable, enlarged and tender over a considerable period of time. Enlargement of the liver, however, has been reported as occurring rather frequently in severe cases of juvenile diabetes (Hanssen [25]; Marble et al.[36]). Functional tests practicable in diabetes did not reveal significant damage of the liver. There was no jaundice at any time, nor were the concentrations of bile and its derivatives in blood and urine abnormal. The stools were carefully studied. No undigested food residuals suggesting impairment of the external secretion of the pancreas could be discovered, although at times the diet contained large amounts of starch and particularly of fat. There were no findings to suggest the diagnosis of hemochromatosis. There was no evidence of allergic reactions, the only skin manifestations being edema while very large doses of insulin were used, and occasional furuncles.

The question of the relationship between the high fever or its causes and the insulin resistance is more difficult to decide. Most of the time the elevations of temperature were coincident with the presence of furuncles. For other short periods of fever no obvious cause could be discovered. They were thought to be due to upper respiratory infections. We are not inclined to consider these infections as the chief or even as the essential cause of the insulin resistance in the present case. First, the insulin resistance was no less at periods when the temperature, the white blood count and the blood sedimentation rate were normal and no evidence of local or general infection could be demonstrated. Secondly, intercurrent infections, especially of the skin, are of frequent occurrence in ill-controlled cases of diabetes without creating insulin resistance of such a degree. For these reasons it is our belief that our patient should be classified under the heading: "Insulin resistance without demonstrable cause."

One can only theorize as to the mechanisms underlying the phenomenon of insulin resistance, e.g., it may be that the injected insulin is not absorbed from under the skin. The observation of insulin resistance coincident with allergic skin reactions points in this direction. There is, however, no conclusive proof of this interpretation. In our case, the fact that large wheals resulting from the injection of 10 c.c. or more of insulin disappeared in a very short time would rather suggest that the rate of absorption was not abnormally slow. Somewhat related to this idea is the hypothesis that appreciable amounts of injected insulin are lost through the kidneys. Experimental evidence is against this assumption. Athanasiou and Reinwein [7] could not prove any relationship between the effectiveness of insulin and insulinuria; Glassberg and his associates [22] were unable to recover any insulin from the urine of their insulin resistant case even after the injection of 900 units within 12 hours. Root and Riseman [41] draw attention to the fact that their two patients remained anuric for several hours while unusually large doses of insulin were given and, therefore, no insulin could be lost through excretion.

Another explanation for the ineffectiveness of insulin may be the existence of

substances in the blood or in the tissues which destroy the insulin or inhibit its action. Watson and Dick [46] tested diabetic and non-diabetic urines for insulin-inhibiting substances and claimed that the urine of diabetics showed stronger inhibition of the insulin action. Karelitz and his associates [30] stated that human blood when mixed with insulin inhibits its action in rabbits. The demonstrated inactivation was greater with diabetic blood than it was with blood of normal persons. De Wesselow and Griffiths [15] found that the blood plasma of some elderly, obese, glycosuric patients, when injected into rabbits diminished the hypoglycemic action of insulin. Marble [35] saw no such effect from serum of his insulin resistant patient. In order to determine the degree of insulin inactivation produced by the blood of our patient, we thoroughly mixed 10 units of insulin with 5 c.c. of the blood and incubated the mixture for 60 minutes at 37° C. Controls of blood from normal persons were prepared in the same way. Both solutions, when injected into rabbits, produced a fast drop of blood sugar and severe insulin reactions. Looking at these experiments in retrospect we have to admit that they were incomplete. It is possible, though not likely, that with decreasing amounts of insulin a difference would have been observed between the blood of our patient and that of normal persons.

Karelitz and his co-workers [29] stated that "blood from patients with purulent infections or artificially produced infection-like conditions . . ., causes greater insulin inactivation . . . than does normal blood." They also found that "blood cells from a patient with myeloid leukemia and pus also show greater insulin inactivating power than do normal cells." They are inclined to hold an enzyme or an enzyme-like substance responsible for this fact. Zeckwer,[52] on the other hand, reports variable results as to insulin inactivation in rabbits during leukocytosis induced by sodium nucleinate. Altogether the evidence of the presence of insulin inactivating substances in the circulating blood in infectious diseases or during leukocytosis does not seem to be very conclusive.

Attempts have been made to explain the phenomenon of insulin resistance by employing certain theories which were developed to explain the normal insulin action. Although assuming different mechanisms, several students of the subject agree that insulin acts as an activator of an enzyme present in the muscles and in other tissues (Brugsch and Horsters,[9] Lundsgaard et al.,[33] Ahlgren [2]). It has been suggested that the different reactions to insulin may be due to the lack of this supposed enzyme. This idea has been expressed in a recent paper by Himsworth,[27] who thinks with others that sensitivity to insulin means lack of endogenous insulin, resistance lack of the factor which renders the insulin effective. His ideas differ from those of others inasmuch as he assumes that insulin is not the activating but the activated principle in this reaction.

Finally, it may be mentioned that within recent years another group of substances has been recognized as being antagonistic to the action of insulin. They are the hormones of the pituitary [28] and adrenal [32] glands. Cope and Marks [12] stated that a suitable extract of the anterior lobe of the pituitary gland produced resistance to insulin. Young [51] is also inclined to assume that the "insulin insensitive type of Himsworth" is due to hypersecretion of a hypophyseal factor rather than to the lack of an insulin sensitizing agent. Long [32] states that anterior pituitary extracts are effective in the absence of the pancreas, and he therefore denies the possibility that a direct neutralization of insulin is the manner by which their "diabetogenic" action is produced.

Our case and our observations do not shed any light on these interesting but still undecided problems.

Summary and Conclusions

1. The expression "insulin resistance" should be reserved for cases which require administration of at least several hundred units of insulin while on a diabetic diet and in which the carbohydrate equivalent is less than 0.5 gram.

2. Reports in the literature and our observations support the assumption that absolute insulin resistance does not occur. Even in cases which at first view seem to be absolutely insulin resistant, some insulin action can be demonstrated.

3. Therefore, insulin resistance is not an indication to discontinue the administration of insulin.

4. The case discussed progressed under our observation from a mild diabetic responding normally to insulin into a severe state of insulin resistance.

5. In the stage of insulin resistance 124,915 units of insulin were given in 3,037 injections during 280 days. In the same period 42,330 grams of sugar were excreted. The largest amount of insulin injected intramuscularly within 24 hours was 1,630 units. The highest fasting blood sugar was 892 mg. per 100 c.c.

6. In addition to certain disorders which are known occasionally to precipitate insulin resistance there are cases in which it arises from unrecognized causes.

7. The mechanisms underlying insulin resistance are still unknown.

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EDITORIAL

EXTRA-HUMAN SOURCES OF POLIOMYELITIS VIRUS

ALTHOUGH the pathway of infection in poliomyelitis has long been a matter of controversy, until recently it was generally believed to be usually the nasal olfactory mucosa, the olfactory tracts and bulbs, from which the virus spreads by direct extension to the motor areas of the brain and spinal cord. Infection was thought to be acquired by droplet infection or direct contact, usually from carriers or unrecognized subclinical cases of the disease. This view has been maintained by Flexner and his associates, based largely on their studies of experimental infections in monkeys.

More recent work, however, has cast doubt on the validity of this view as far as human infection is concerned, and points strongly to the alimentary tract as the usual portal of entry of infection. Some of the more important observations on which this view is based have already been discussed.[1] As previously pointed out, there is ample proof that in many cases, at least, virus is present in the feces in large amounts, and that it can remain viable in feces and in contaminated sewage for substantial periods of time. This manifestly constitutes an important possible source of infection, if the view is confirmed that man may be infected through the gastrointestinal tract. In that event, the mode of dissemination of the disease might be expected to resemble that of typhoid fever rather than a respiratory tract infection and opportunities for fecal contamination of foods would be epidemiologically important.

The recent demonstration that flies may be carriers of the virus is, therefore, of great interest. Although several isolated successful attempts were reported in 1911 and 1912, adequate confirmation was not obtained until 1941, when Toomey et al., Paul, Trask, et al., and Sabin and Ward independently reported the demonstration of the virus in washings or emulsions of flies trapped near houses which were harboring or had recently harbored cases of the disease. Sabin and Ward [2] reported eight positive results out of 15 samples examined, and Trask, Paul and Melnick [3] obtained four positive out of 19 samples tested. In most cases the flies had access to feces which presumably may have contained virus. No evidence was obtained that the flies were more than passive carriers, nor is there evidence as yet that human cases have actually been infected from this source.

The possibility that other mammals might serve as a reservoir of infection hitherto has received little consideration because (except for the

[1] The pathway of infection in poliomyelitis, Editorial, ANN. INT. MED., 1941, xv, 329–332.
[2] SABIN, A. B., and WARD, R.: Insects and epidemiology of poliomyelitis, Science, 1942, xcv, 300.
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monkey) the ordinary domestic and laboratory animals are usually quite resistant to inoculations of the virus. In a few cases, however, infections with certain strains of poliomyelitis virus have been established in white mice. In 1939 Armstrong was able to convey a freshly isolated human strain ("Lansing" strain) of virus from a monkey to cotton rats, and after infection was well established in the rats to carry it on in white mice. In 1940 Jungeblut and Sanders [4] were able in three different series of animals to convey the SK New Haven strain of poliomyelitis virus in a similar manner from monkeys to cotton rats, and then to white mice. In 1941 Toomey also was able to establish infection in white mice with the RMV strain of virus. These were accomplished only with much difficulty, however, and many unsuccessful attempts have been made to infect mice with other strains.

After the infection was once established in mice,[4] the virus showed some alteration as a result of its adaptation to this species. Its virulence for mice increased greatly, so that the animals could be infected by highly diluted (one to one billion) virus suspensions, and by peripheral as well as by intracerebral inoculation. They could also be infected by feeding the virus. With this increase in virulence for mice, however, there was a more or less marked reduction or even a nearly complete loss of virulence for monkeys. There were also some changes in the immunological reactions of the virus. It seemed probable, however, that the mouse-adapted strain of virus represented a variant or mutant of the original strain rather than a specifically different virus. The histological lesions produced in mice were typical of poliomyelitis and the immunological reactions indicated at least a close group relationship. These observations, however, would give no basis for the expectation that such a virus would be readily passed back and forth from mice to man.

Recent observations of Jungeblut and Dalldorf,[5] however, indicate that this possibility must receive serious consideration, at least for some strains of virus. They studied an epidemic of poliomyelitis occurring in a circumscribed area in White Plains, N. Y., and consisting of five cases of which two were fatal. In the basement of the house in which one patient had died, they found one freshly dead gray mouse, and they trapped a considerable number of live mice in this and other houses in the area. By intracerebral inoculation of albino mice they demonstrated a virus in the brains of three of the captured gray mice, including the one found dead. The affected animals showed symptoms of encephalitis which in some progressed to paralysis and death. Two of the virus strains died out, but the third (from the dead mouse) was established successfully in white mice, with increase in virulence. It also infected cotton rats and hamsters, but not rabbits, guinea pigs or rhesus monkeys. The agent was filtrable. It produced lesions in the brains

[4] JUNGEBLUT, C. W., and SANDERS, M.: Studies of a murine strain of poliomyelitis virus in cotton rats and white mice, Jr. Exper. Med., 1940, lxxii, 407–436.

[5] JUNGEBLUT, C. W., and DALLDORF, G. T.: Epidemiological and experimental observations on the possible significance of rodents in a suburban epidemic of poliomyelitis, Am. Jr. Pub. Health, 1943, xxxiii, 169–172.

of the mice identical with those caused by known strains of poliomyelitis virus. It was inactivated by the serum of the three convalescent human cases.

A virus was also isolated from the brain of one of the human cases by successive intracerebral inoculation in a monkey, a hamster, and in white mice. This virus was described as similar in all respects to the strain obtained from the gray mouse except in the higher degree of virulence which it attained. It was also neutralized by sera from the three convalescent human cases, and in varying degree by antisera to Theiler's mouse encephalomyelitis virus, to the SK murine strain of poliomyelitis virus, and to a monkey poliomyelitis virus. The authors conclude that the virus belongs to the poliomyelitis group of viruses, and is possibly related to Theiler's mouse encephalomyelitis virus.

The results of these experiments must be interpreted with caution. It seems improbable that the virus strains obtained were simply contaminants, although this is perhaps not entirely excluded. It seems highly probable that the virus strains obtained from the mice and the human case were identical. Their identity with ordinary strains of human poliomyelitis virus is much more questionable, particularly those which have resisted adaptation to mice. They do indicate the need of further intensive study of these questions, and suggest the possibility that in some cases human infection might result from the contamination of food by the excreta of infected mice.

REVIEWS

Heart Failure. By ARTHUR M. FISHBERG, M.D., 2nd edition. 829 pages; 15.5 × 24 cm. Lea & Febiger, Philadelphia. 1940. Price, $8.50.

Incorporating advances made in the field since the first publication, the second edition of this fine book holds a vast amount of information for those interested in the cardiovascular system. The material is well ordered and clearly presented and no aspect of circulatory failure seems to be omitted. The physiologic mechanisms regulating changes in the circulation and the basis for the various symptoms and signs in failure are covered in detail. Physiology is related to clinical cardiology in the discussions of failure in various cardiac affections and in the rationalization of treatment. There is a large bibliography with well incorporated references, and the table of contents and index are full enough so that desired topics can be found. The book therefore serves as an unique reference work on circulatory failure and is highly recommended as authoritative in this field.

C. E. L.

Tables of Food Values. By ALICE V. BRADLEY, M.S. 224 pages; 20 × 25.5 pages. The Manual Arts Press, Peoria, Ill. 1943. Price, $3.50.

This book has been completely revised, enlarged and brought up-to-date with the most recent scientific information pertaining to the nutritive value and composition of foods. It is divided into four sections.

Section I briefly and clearly discusses the most important factors in the composition of an adequate diet. The carbohydrates, fats, proteins, and body regulators (minerals, vitamins, cellulose, and water) are each explained as to composition, body requirements, and body function. Body requirements and availability of each of the essential minerals and vitamins are discussed in non-technical terms.

The second section emphasizes the points to consider in diet calculation and menu planning. A list of foods which should be included in the daily adequate diet is given. The factors which determine one's caloric requirement and the method of computing an individual's daily caloric requirement may be easily understood. Rules to be considered in planning well-balanced and tempting meals are listed with examples. A chart of the daily allowances of specific nutrients recommended by the National Nutritional Conference in Washington, D. C. in 1941 is given.

Section III consists of charts showing the food values of average servings of common foods expressed in grams and household measures. The amounts of protein, fat and carbohydrate are listed in grams, the minerals in shares, and the vitamins in Internation Units or milligrams. Recipes accompany many of the tables, such as those of cakes and ice cream.

Section IV is composed of tables showing the food values of 100 gram portions instead of average servings of the same foods in the third section. This is valuable for accurate calculation of weighed diets.

For anyone interested in the composition and nutritive values of foods or in computing diets with accuracy, this book is sufficient with no other reference necessary.

E. F.

BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Memoir of Walter Reed. The Yellow Fever Episode. By ALBERT E. TRUBY, Brigadier General, United States Army, retired. 239 pages; 20 × 13.5 cm. 1943. Paul B. Hoeber, Inc., New York, N. Y. Price, $3.50.

Methods of Treatment. Eighth Edition. By LOGAN CLENDENING, M.D., and EDWARD H. HASHINGER, A.B., M.D. 1033 pages; 25 × 17 cm. 1943. C. V. Mosby Co., St. Louis, Missouri. Price, $10.00.

A Synopsis of Clinical Syphilis. By JAMES KIRBY HOWLES, B.S., M.D., M.M.S. 671 pages; 20 × 13.5 cm. 1943. C. V. Mosby Co., St. Louis, Missouri. Price, $6.00.

Rehabilitation of the War Injured. A Symposium. Edited by WILLIAM BROWN DOHERTY, M.D., and DAGOBERT D. RUNES, Ph.D. 684 pages; 23.5 × 16 cm. 1943. Philosophical Library, Inc., New York, N. Y. Price, $10.00.

El Pulso Venoso Normal. (Tesis de Doctorado en Medicina.) By AGUSTÍN CAEIRO. 148 pages; 23 × 16 cm. 1943. Sebastián de Amorrortu e Hijos, Buenos Aires.

Handbook of Tropical Medicine. By ALFRED C. REED, M.D., and J. C. GEIGER, M.D. 188 pages; 17 × 12 cm. 1943. Stanford University Press, Stanford University, California. Price, $1.50.

Addendum to the Chemistry of the Amino Acids and Proteins. Edited by CARL L. A. SCHMIDT, M.S., Ph.D. 1290 pages; 26 × 17 cm. 1943. Charles C. Thomas, Springfield, Illinois. Price, $5.00.

Gastro-Enterology (in three volumes). Volume I: *The Esophagus and the Stomach.* By HENRY L. BOCKUS, M.D. 831 pages; 25.5 × 17 cm. 1943. W. B. Saunders Co., Philadelphia. Price (three volumes), $35.00.

Borderlands of Psychiatry. (Harvard University Monograph in Medicine and Public Health—No. 4.) By STANLEY COBB, Bullard Professor of Neuropathology, Harvard Medical School; Psychiatrist in Chief, Massachusetts General Hospital. 166 pages; 23.5 × 16 cm. 1943. Harvard University Press, Cambridge, Massachusetts. Price, $2.50.

COLLEGE NEWS NOTES

Additional A. C. P. Members in the Armed Forces

Already published in preceding issues of this journal were the names of 1,453 Fellows and Associates of the College on active military duty. Herewith are reported the names of 18 additional members, bringing the grand total to 1,471.

Kenneth D. A. Allen
Horace M. Banks
Asher S. Chapman
Cyrus J. Clark
William R. Galbreath
Emil H. Grieco
William E. Hall
Joseph F. Jenovese
H. Beckett Lang
Thomas A. Lebbetter
George W. Lynch
Ralph Lynch
John F. McManus
Robert S. Palmer
Lucian A. Smith
Lydon H. Thatcher
Louis D. Vaughn
Philip Work

Gifts to the College Library

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

Dr. Jacob C. Geiger, F.A.C.P., San Francisco, Calif.—"Handbook of Tropical Medicine."

Reprints

Dr. Guy H. Faget, F.A.C.P., U. S. Public Health Service, Carville, La.—1 reprint;
Dr. James M. Flynn, F.A.C.P., Rochester, N. Y.—1 reprint;
Irving Greenfield, F.A.C.P., Captain, (MRC), U. S. Army—1 reprint;
Dr. John F. Kenney, F.A.C.P., Pawtucket, R. I.—1 reprint;
Dr. Richard E. DeMonbrun Kepner, F.A.C.P., Honolulu, T. H.—2 reprints;
Horace Page Marvin, F.A.C.P., Lieutenant Colonel, (MC), U. S. Army—1 reprint;
Dr. Thomas H. McGavack, F.A.C.P., New York, N. Y.—1 reprint;
Dr. Frederick W. Mulsow, F.A.C.P., Cedar Rapids, Iowa—2 reprints;
Dr. William H. Ordway, F.A.C.P., Mount McGregor, N. Y.—1 reprint;
Dr. Dudley C. Smith, F.A.C.P., University, Va.—11 reprints;
Leon H. Warren (Associate), Major, (MRC), U. S. Army—1 reprint.

Schedule of Examinations by Certifying Boards

American Board of Internal Medicine:
William A. Werrell, M.D., Assistant Secretary
1301 University Ave.
Madison, Wis.

Written Examination: October 18, 1943. Will be held in various cities and may be arranged at some Army and Navy stations with the approval of medical commanding officers.

Oral Examination: Communicate with the Assistant Secretary for schedule of examinations in various parts of the country. During the war, oral examinations are held at various times in New Orleans, San Francisco, Philadelphia and other cities.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY: C. Guy Lane, M.D., Secretary 416 Marlboro St. Boston, Mass.	*Written Examination:* Various cities, September 27, 1943. *Oral Examination:* Philadelphia, November 5–6, 1943.
AMERICAN BOARD OF PEDIATRICS: C. A. Aldrich, M.D., Secretary 707 Fullerton Ave. Chicago, Ill.	*Written Examination:* October 8, 1943 (locally, under a monitor). *Oral Examination:* New York, N. Y., November 20–21, 1943.
AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: Walter Freeman, M.D., Secretary 1028 Connecticut Ave., N. W. Washington, D. C.	*Written Examination:* October 30, 1943, locally. *Oral Examination:* December 20–21, 1943, locally. Final date for filing application, September 30, 1943.

REGIONAL MEETINGS OF THE COLLEGE

The Northwest Regional Meeting

A Regional Meeting for the states of Washington, Oregon and Idaho, and for the provinces of Alberta, British Columbia, Manitoba and Saskatchewan, will be held at Seattle, Wash., September 24, 1943, under the General Chairmanship of Dr. Edwin G. Bannick, Acting Governor for Washington, and under an Executive Committee consisting of Dr. Homer P. Rush, Governor for Oregon, Dr. Samuel M. Poindexter, Acting Governor for Idaho, and Dr. George F. Strong, Governor for the Southwestern Provinces of Canada.

The meeting will consist of clinical presentations in the morning, general sessions in the afternoon, and a dinner meeting in the evening. Meetings will be held on the University of Washington campus, where excellent facilities are available. The evening dinner meeting will be addressed by Dr. Ernest E. Irons, President-Elect, of Chicago, Brigadier General David N. W. Grant, Air Surgeon of the U. S. Army Air Forces, Washington, D. C., Brigadier General Hugh J. Morgan, of the Office of the Surgeon General, U. S. Army, Washington, D. C., Rear Admiral W. L. Mann, Commandant, Thirteenth Naval District, Seattle, Colonel Wallace Wilson, Command Medical Officer, Pacific Command, Royal Canadian Army Medical Corps, and others.

A formal program may be obtained from the Executive Offices of the College.

All medical officers of the Armed Forces of the United States and Canada are cordially invited, whether members of the College or not. The Regional Meeting of the College will be followed by a meeting the succeeding day of the North Pacific Society of Internal Medicine.

North-Central States Regional Meeting

A Regional Meeting, embracing Illinois, Indiana, Iowa, Michigan and Wisconsin, will be held at the Drake Hotel, Chicago, October 16, 1943, under the General Chairmanship of Dr. LeRoy H. Sloan, College Governor for Northern Illinois and under an Executive Committee of the Governors for the participating regions, including Dr. Cecil M. Jack, Decatur, Ill., Dr. Robert M. Moore, Indianapolis, Ind., Dr. Benjamin F. Wolverton, Cedar Rapids, Iowa, Dr. Patrick L. Ledwidge, Detroit, Mich., and Dr. Elmer L. Sevringhaus, Madison, Wis.

Formal program will be ready for distribution September 20, 1943. All medical officers of the Armed Forces, in addition to members of the College, are cordially invited.

Chicago Regional Meetings of the College in the past have been exceptional. Attendance has been large and the programs have been of the best. It is anticipated that this meeting will be most successful.

It so happens that a postgraduate course in Endocrinology, arranged by the College under the direction of Dr. Willard O. Thompson at the Presbyterian Hospital, will be given during the preceding week, from October 11, and all physicians taking that course are invited to participate in the Regional Meeting of the College.

The Philadelphia Round-Up

The 6th Annual Regional Meeting of Eastern Pennsylvania, New Jersey, Delaware, and adjacent territory, will be held at Philadelphia, Friday, November 19, 1943, under the General Chairmanship of Commander Edward L. Bortz, (MC), U. S. Naval Reserve, College Governor for Eastern Pennsylvania, and with the assistance of the Governors of the participating regions, including Dr. George H. Lathrope, Governor for New Jersey, and Dr. Lewis B. Flinn, Governor for Delaware. The morning will be devoted to a special program arranged by Dr. O. H. Perry Pepper of the Hospital of the University of Pennsylvania, followed by a buffet luncheon at the College Headquarters at 4200 Pine St.; an afternoon general session in the ballroom of the Benjamin Franklin Hotel, Ninth and Chestnut Sts.; and an evening cocktail party-dinner meeting at the Hotel. Significant on the afternoon program will be presentations by medical officers from the Army and Navy of the United States and Canada who have had first-hand experience in the war zones and in rehabilitation and care of the wounded.

It is expected that several dignitaries from the Army and Navy, as well as from the general profession, will be on the program at the dinner meeting in the evening.

As already published in the August issue of this journal, a postgraduate course in Special Medicine will be given at Philadelphia institutions during the preceding two weeks, and the program will terminate in this Regional Meeting. Therefore, invited to the meeting are all members of the College, all registrants in the postgraduate course in Special Medicine, and all medical officers in the Armed Forces and others who may be especially interested in any feature in the program.

A. C. P. Postgraduate Courses

The Postgraduate Bulletin of the College, containing the list of its courses offered in the autumn, 1943, is ready for distribution. The schedule calls for the following three courses and the Bulletin gives the detailed data concerning each. Address inquiries to the Executive Secretary, 4200 Pine St., Philadelphia, Pa.

Course No. 1—Endocrinology
(October 11–16, 1943)
University of Illinois College of Medicine and the
Presbyterian Hospital
1753 W. Congress St., Chicago, Ill.
Willard O. Thompson, M.D., F.A.C.P., *Director*
Fee, $20.00

Course No. 2—Allergy
(October 25–30, 1943)
Roosevelt Hospital, New York, N. Y.
Robert A. Cooke, M.D., F.A.C.P., *Director*
(Minimal Registration, 25; Maximal Registration, 50)
Fee, $20.00

COURSE No. 3—SPECIAL MEDICINE
(November 8–19, 1943)
Philadelphia Institutions
CHARLES L. BROWN, M.D., F.A.C.P., *Director*
Fee, $40.00

Colonel Edgar Erskine Hume, (MC), U. S. Army, (F.A.C.P.), has been appointed Health Officer of Occupied Sicily, in connection with the Allied Military Government of Occupied Territory.

Lieutenant Colonel Charles T. Young, (MC), U. S. Army (Associate), was awarded the Legion of Merit for exceptionally meritorious service in the performance of his duties during and after the Japanese attack on Oahu, December 7, 1941. Colonel Young was Chief of the Medical Service. The citation indicated that by his excellent judgment and thorough adaptability he reflected great credit on the Medical Corps of the U. S. Army. Colonel Young has been an Associate of the American College of Physicians since 1939.

Captain E. David Sherman, R.C.A.M.C., (Associate), Sydney, N. S., Canada, has been appointed Abstract Editor of the Nova Scotia Medical Bulletin and Consultant in Cardiology to the Marine Hospital at Sydney.

Lieutenant Mack Leonard Gottlieb, (MC), U. S. Naval Reserve, an Associate of this College, was taken prisoner at Guam and is now interned at the Zentsuji War Prison Camp, Shikoku, Japan.

The Air Medal was conferred August 4, 1943, on Major Aaron A. Sprong, (F.A.C.P.), Post Flight Surgeon at the Strother Army Air Field, Kan. Major Sprong was cited for "meritorious achievement while participating in an air flight on December 16, 1942, over the Solomon Islands. Major Sprong was Flight Surgeon for the No. 5 wingman in a successful bombing mission with a flight of six B–17 airplanes. Sixteen enemy fighters attacked the formation and the No. 3 wingman was disabled early in the encounter. No. 5 wingman remained with the injured plane until it crash-landed although he, too, had lost one engine in the encounter. The action by the No. 5 wingman helped to prevent the complete destruction and loss of No. 3 wingman from enemy action. The crew was later rescued. At least four enemy fighters were destroyed."

SCHOOL OF MILITARY GOVERNMENT ESTABLISHED AT THE UNIVERSITY OF VIRGINIA

The School of Military Government has been established, under the auspices of the Provost Marshal General's Office of the War Department, at Charlottesville, Va. It is designed to prepare officers for future detail in connection with military government and liaison.

Each class of the School is made up entirely of commissioned officers of the grades of Captain to Colonel. Applications are not considered from persons not in the military service. Students are selected by the War Department following recommendations of the Commandant and the Provost Marshal General. In evaluating qualifications, much weight is given to experience in a former military government and in the Federal Government, or in the government of a state, county or city, and to professional training in government and public administration. Importance is

attached to demonstrated administrative and executive ability and to a knowledge of foreign languages and countries.

Officers on active duty are selected from recommendations made by higher commanders and chiefs of services and others. They may also apply for admittance to the School by letter addressed to the Provost Marshall General, through proper channels. All applications should give complete information as to age, education, training and experience, both military and civilian. Inquiries concerning commissions should be directed to the nearest office of Officer Procurement Service.

Major Leon H. Warren (Associate), M.C., U. S. Army, delivered an address on Military Dermatology, July 16, to the students of George Washington University Medical School in a special series of lectures on the professional aspects of military medicine.

Dr. James D. Bruce, F.A.C.P., Ann Arbor, Mich., has established the Theodore A. McGraw Memorial Scholarship, to be awarded to the outstanding junior in Wayne University College of Medicine, Detroit, in memory of the late Dr. McGraw, who was formerly President of the College when it was known as the Detroit College of Medicine and Surgery. The award is in the amount of $100.00 annually.

Dr. Victor Johnson, Associate Professor of Physiology and Dean of Students in the Division of Biological Sciences, University of Chicago, was appointed on July first Secretary of the Council on Medical Education and Hospitals of the American Medical Association.

Dr. Josiah J. Moore, F.A.C.P., Chicago, has been elected Vice President of the American Society of Clinical Pathologists.

Dr. Edward Urbane Reed, F.A.C.P., District Medical Officer of the Third Naval District, has received executive nomination for the rank of Rear Admiral.

Dr. Joseph A. Capps, F.A.C.P., Chicago, was the founder of the Joseph A. Capps Prize offered annually by the Institute of Medicine of Chicago "for the most meritorious investigation in medicine or in the specialties of medicine." The investigation may also be in the fundamental sciences, provided the work has a definite bearing on some medical problem. Graduates of Chicago medical schools who completed an internship or one year of laboratory work in 1941 or thereafter may enter competition. Manuscripts must be submitted not later than December 31 to the Institute, 86 E. Randolph Street, Chicago.

Dr. James E. Paullin, F.A.C.P., President of the American College of Physicians, Atlanta, Ga., and Dr. Tom D. Spies, F.A.C.P., of Birmingham, Ala., will appear on the program of the Eleventh Annual Assembly of the Omaha Mid-West Clinical Society, October 25–29.

Dr. Philip Work, F.A.C.P., has resigned as Professor of Neurology and Head of the Department at the University of Colorado School of Medicine, Denver, and is now on active duty in the Medical Corps of the U. S. Army as a Lieutenant Colonel.

Dr. Clough T. Burnett, F.A.C.P., has resigned from the same institution as Associate Professor of Medicine.

As a memorial to the late Dr. Walter R. Steiner, F.A.C.P., Hartford, Conn., Mr. Elisha H. Cooper, New Britain, Conn., has furnished a room adjoining Yale University's Historical Library. In this room will be housed medical memorabilia, including items of historical interest presented by Dr. Steiner during his life time.

Upwards of one and three-quarter millions of dollars will eventually go to the University of Rochester as a fund for research in Internal Medicine, as provided in the will of Mrs. Bertha H. Buswell, of Buffalo.

Dr. Cecil J. Watson, F.A.C.P., Minneapolis, Minn., has been appointed Head of the Department of Medicine and Director of the Division of Internal Medicine at the University of Minnesota Medical School.

Dr. Alphonse E. Walch, F.A.C.P., Minneapolis, Minn., has been promoted at the University to Clinical Assistant Professor of Medicine.

Colonel Edgar Erskine Hume, F.A.C.P., of the U. S. Army Medical Corps, and Dr. Tomas Cajigas, F.A.C.P., Washington, D. C., were recently awarded the medal of the Aztec Eagle for work on military medicine. Both are honorary members of the Academia Nacional de Medicina of Mexico.

According to the Journal of the American Medical Association, the Southwestern Medical Foundation School of Medicine was opened June 21 at Dallas for the registration of students. This new school originated through the Southwestern Medical Foundation, which is chartered to carry on medical education and research. This school is using temporary buildings until permanent buildings may be erected on the twenty-five acre campus, which has already been purchased. It is estimated that the entire project will have an initial fund of one million, five hundred thousand dollars to start, and that eventually ten million dollars will be expended and a fifteen million dollar endowment established. Dr. Edward H. Cary is President and Dr. Don H. Slaughter is Acting Dean of the Medical School.

Dr. Ralph K. Hollinshed, F.A.C.P., Westville, N. J., was recently installed as President of the Medical Society of New Jersey.

Dr. Walter E. Vest, F.A.C.P., Huntington, W. Va., has been reappointed by Governor Neely as a member of the Public Health Council for the term ending June 30, 1947. Since 1937 Dr. Vest has been President, and since 1933 a member of the Council.

Dr. Anthony Bassler, F.A.C.P., New York City, Dr. Clarence J. Tidmarsh, F.A.C.P., Montreal, and Dr. Harry M. Eberhard (Associate), Philadelphia, have been re-elected, respectively, President and Vice Presidents of the National Gastro-Enterological Association.

Announcement is made in a recent issue of the Journal of the Medical Association of Georgia concerning the Oglethorpe University School of Medicine, which is now seeking accreditation of the Council on Medical Education and Hospitals of the American Medical Association. The school is entering its third academic year, quarters have been built or remodeled for the departments of microscopic and gross

anatomy, biological chemistry and laboratory medicine, physiology, pharmacology, pathology and bacteriology. A Clinic has been built and organized in down-town Atlanta, to aid in teaching third year students.

Dr. Charles C. de Gravelles, F.A.C.P., New Iberia, La., was recently installed as President of the Louisiana State Medical Society.

Dr. M. D. Hargrove, F.A.C.P., Shreveport, La., was elected First Vice President.

Dr. Oscar W. Bethea, F.A.C.P., New Orleans, La., was recently installed as President of the New Orleans Graduate Medical Assembly.

The Medical School and the Woman's College of Duke University, Durham, N. C., will open on September 27 a School of Physical Therapy, the school to be conducted at Duke Hospital.

Dr. Thomas H. A. Stites, F.A.C.P., recently resigned as Medical Director of the State Tuberculosis Sanatorium at Cresson, Pa., after twenty-nine years of service to the State.

Dr. T. Dewey Davis, F.A.C.P., Richmond, Va., was recently elected President of the Richmond Tuberculosis Association, filling the unexpired term of Captain Fred W. Scott, who resigned. Dr. Davis has served as a member of the Board of Directors for many years, has been Chairman of the Medical Committee and the annual early diagnosis campaign, and also a member of the Executive Committee.

Harvard Medical School, Courses for Graduates, has announced that it will conduct a condensed one-day conference and a more extensive seminar in legal medicine. There has been a steadily increasing demand for instruction in this subject, and the facilities have been relatively limited in this country. No attempt will be made to turn out expert medico-legal specialists, but rather the aim will be to give to the average medical examiner, coroner, or other physician interested in the subject, a better general working knowledge, in order that he can better perform his day-to-day duties.

The course was initiated last year and was sufficiently popular to be repeated one month later. The course will be held at the Mallory Institute of Pathology, Boston City Hospital, Wednesday, October 6, 1943, and will be open to any registered physician, lawyer, police official, criminal investigator, senior medical student, or other person whose duties are associated with medico-legal topics.

There is no fee. An advance application is not essential. However, advance notice of intention to attend will be helpful, if addressed to Dr. William H. Watters, F.A.C.P., Department of Legal Medicine, Harvard Medical School, Boston.

There will be offered also a Seminar in Legal Medicine during the entire week of October 4–9, inclusive. This is planned particularly for medical examiners and coroners' physicians, but will be open also to any other suitable graduate of an approved medical school.

The fee will be $25.00. An application should be made on or before October 1 to Harvard Medical School, Courses for Graduates, Boston, Mass.

REPORT OF CENTRAL COMMITTEE FOR WAR-TIME GRADUATE MEDICAL MEETINGS

The Central Committee of War-Time Graduate Medical Meetings respectfully submits the following as a report of its endeavors and accomplishments since the inception of the Committee and the organization of a central office:

The Committee was officially commissioned to proceed with its plans on February 18, 1943, and a central office opened at 4200 Pine Street, Philadelphia, on March 1.

Since the beginning of the work, three meetings of the Central Committee have been held: March 14–15, in New York City; April 4, in Philadelphia; and June 26, in Philadelphia.

As a means of introduction, the Committee drew up a Statement of Organization as of March 1, which was later revised as of May 1. This Statement of Organization, together with a map showing the twenty-four regional districts into which the country had been divided and the lists of National Consultants and Regional Committee members, was widely distributed to all the key-men throughout the entire country, including the National Consultants and Regional Committee members.

On March 15, through Dr. Herman Weiskotten, then Secretary of the Council on Medical Education and Hospitals of the American Medical Association, the deans of all the medical schools of the country were contacted in the hope of enlisting their interest in and cooperation with the War-Time Graduate Medical Meetings. From fifty-five of the deans, enthusiastic replies have been received. The names of teachers from these medical schools, who will be available and eager to participate in this program, are now on file in the central office.

The Chairman of the Central Committee has met with representatives of the Rockefeller Foundation and the Commonwealth Fund and discussed the project with them.

Meetings at which the Central Committee of the War-Time Graduate Medical Meetings has already offered the facilities at its disposal include the Georgia State Medical Association Meeting which was held on May 13, 1943, at which Drs. James Means, Virgil P. Sydenstricker and William H. Evans appeared at the invitation of the Committee.

Also on May 3–5, Drs. Edwin E. Osgood and L. T. Coggeshall participated in a Refresher Course, at the invitation of the War-Time Graduate Medical Meetings, offered by the University of Alberta Hospital in Edmonton, Alberta, Canada.

The Regional Committees, to date have responded as follows:

Region No. 1—Maine, New Hampshire, Vermont, Massachusetts, and Region No. 2—Connecticut and Rhode Island, have consolidated their activities and will work in cooperation with the First Service Command and the Naval District in the New England States. Plans are nearing completion for postgraduate courses at the Newport Naval Hospital for September 14–15–16, including a one-day presentation of medical subjects, one day of surgical subjects and one day of subjects in the various fields of medicine. Approximately twenty-five speakers will be presented.

Plans are likewise being formulated for a one, two or three day program to be presented at New London in October.

This committee is also working in cooperation with the committee arranging the Clinical Congress of the 19th Clinical Congress of the Connecticut State Medical Society to be held on September 28–29.

Region No. 3—New York: Courses have already been conducted and others now being formulated. On July 23, a program covering the "Diagnosis and Treatment of Cardiac Pain" was presented at the St. Albans Naval Hospital; on July 27, a two-hour lecture in Chemotherapy was presented at the St. Albans Naval Hos-

pital; and on August 3, a lecture by Dr. Henry Meleny on "Malaria" at the Brooklyn Naval Hospital. Plans are being made for lectures in shock, burns and plasma, and the dysenteries, for some time in September.

Region No. 4—Eastern Pennsylvania, Delaware and New Jersey: The committee is extremely active and while no definite time for courses has yet been decided upon, there will be one or two presented in the early fall.

Region No. 5—Maryland, District of Columbia, Virginia and West Virginia: Interested and active committee in process of planning courses for fall.

Region No. 6—North Carolina, South Carolina: Committee active; held meeting of representatives of all military installations in this region on August 2 to decide upon needs of Medical Officers in this region.

Region No. 7—Georgia and Florida: Committee working on an excellent four week program to be presented at Service installations in Florida in early fall.

Region No. 9—Michigan: Committee proceeding in cooperation with other interested groups to offer post-graduate medical instruction to Medical Officers.

Region No. 10—Kentucky, Tennessee: Committee has planned an excellent course for week of October 3 covering burns, shock, blood derivatives and substitutes; chemotherapy; general surgery and the dysenteries.

Region No. 11—Alabama and Mississippi: Committee proceeding with basic plans best suitable for district which it covers.

Region No. 12—Louisiana: Committee exceedingly interested in program and endeavoring to offer the facilities of the War-Time Graduate Medical Meetings where such need is apparent.

Region No. 13—Texas: Plans for courses have been tentatively made.

Region No. 14—Indiana, Illinois and Wisconsin: Committee doing a superb piece of work in correlating the facilities already available with those offered by the War-Time Graduate Medical Meetings.

Region No. 16—Missouri, Kansas, Arkansas, Oklahoma: Committee proceeding with plans best suited for this district.

Region No. 17—North Dakota, South Dakota, Nebraska: Committee slowly proceeding with plans.

Region No. 18—Montana, Wyoming: Plans proceeding for courses to be offered in the autumn covering the subjects of anesthesia; shock, burns, blood derivatives; clinical psychiatry, psychosomatic medicine; cardiovascular problems; dysenteries; acute respiratory disease, physical therapy, diagnostic roentgenology.

Region No. 19—Colorado, Utah: Plans have been made for programs to be offered on September 30, and October 1, 1943, in Denver.

Region No. 20—New Mexico, Arizona: Plans being made for programs to be submitted in late fall, probably at some central point such as Albuquerque or Santa Fe.

Region No. 23—Nevada, Northern California: Interest in this program is widely apparent in this section of the country.

Region No. 24—Southern California: Rather slow progress; some difficulty in getting started with service hospitals.

No progress reports have as yet been submitted from the following regions:

Region No. 8—Western Pennsylvania and Ohio.
Region No. 15—Minnesota and Iowa.
Region No. 21—Washington.
Region No. 22—Idaho and Oregon.

The National Consultants are now compiling the names of outstanding men throughout the entire country who are willing to serve on a National Faculty. This Faculty will aid the committees in meeting the demands for teachers.

Requests have recently been received in the Central Office for speakers to appear on the program being offered by the Delhousie University for Medical Officers in the Canadian Forces during the week of October 11, and also for the annual meeting of the Saskatchewan Medical Society to be held in Reginia, Saskatchewan, Canada, on September 16, 17, and 18.

Respectfully submitted,

EDWARD L. BORTZ,
Chairman

SPECIAL NOTICE

At St. Elizabeth's Hospital, the Federal institution for the treatment of mental disorders, Washington, D. C., fine opportunities for psychiatric residencies and rotating internships are open to recent graduates of medical schools; these residencies and internships rank among the best in the United States. The Institution has 7,000 patients including members of our armed forces who are casualties of the present war. In order that these men as well as civilian patients receive adequate care and treatment, it is necessary to recruit a number of Junior Medical Officers.

The rotating internship consists of 1 year of rotating service including medicine, surgery, psychiatry, laboratory, pediatrics (affiliation), and obstetrics (affiliation). Applicants must be fourth-year students in a Class A medical school or they must have successfully completed their fourth year of study in a Class A medical school subsequent to December 31, 1935. The duties of Junior Medical Officer (Rotating Internship) are those of an interne assigned to medical, surgical, and laboratory services, and out-patient clinics.

A postgraduate internship of 1 year in psychiatry is offered to graduates of medicine who have already served an accredited rotating internship. Applicants must have successfully completed their fourth year of study in a Class A medical school subsequent to December 31, 1932, and they must have the degree of either B.M., or M.D. In addition, they must have successfully completed an accredited rotating internship of at least one year, except that applications will be accepted from persons now serving such internship. The duties of Junior Medical Officer (Psychiatric Resident) are those of a resident in the diagnosis and treatment of mental patients.

It is possible that women may be utilized in these positions. Appointments to the above positions will be made at various times during the year as vacancies arise. The positions pay $2,000 a year (plus $433 overtime pay). There are no age limits for these positions. No written test is required. Persons now using their highest skills in war work should not apply. Appointments in Federal positions are made in accordance with War Manpower Commission policies and employment stabilization plans.

The Commission would appreciate your bringing this information to the attention of qualified persons who you feel may be interested. An official announcement, amendment, and application forms may be obtained at first- or second-class post offices, Civil Service Regional Offices, and the Commission.

By direction of the Commission:

Very respectfully,

WM. C. HULL,
Executive Assistant

OBITUARIES

DR. JAMES BASSETT McELROY

Dr. James Bassett McElroy died at his home in Memphis, Tennessee, on March 24, 1943. He was 76 years old. In his death the South has lost one of its most distinguished physicians.

He graduated in medicine in 1893 from the College of Physicians and Surgeons of Baltimore, Maryland. For many years he has held a very prominent position in the University of Tennessee College of Medicine, serving as Professor of Medicine, Dean, Chairman of the Faculty, and Member of the Board of Trustees. While he was connected with the Medical School it enjoyed its greatest growth and attained its present high standing among the medical schools of the Country. Much of this progress of the School was due to Dr. McElroy's enthusiastic work in its interest.

In 1902–1903 he was Secretary of the Section on Practice of Medicine of the American Medical Association. He has been President of the Tennessee State Medical Association and of the Memphis and Shelby County Medical Society. He has been a Fellow and also a Governor of the American College of Physicians.

The accomplishments of Dr. McElroy have been many indeed and it is almost impossible to review even briefly the many characteristics of a man who crammed into one life enough work for two average lives. The young student of medicine who is seeking guidance to success in his profession would do well to emulate him. While Dr. McElroy blazed his own trail through life and would want those who come after him to do the same, nevertheless he had many traits that have been outstanding in other big men. He was a good student who was not afraid to work. He was endowed with an unusual amount of vitality. He was human, kind, very fair, methodical, conscientious and thorough.

He believed that the physician should be just a plain good doctor with a lot of real hard sense. He was a staunch friend of physicians who were trying to practice medicine the way it should be practiced and was definitely opposed to those who made little effort to keep abreast of the recent advances in modern medicine.

WILLIAM C. CHANEY, M.D., F.A.C.P.,
Governor for Tennessee

DR. WILLIAM SIMONS OVERTON

Dr. William Simons Overton (Associate), Binghamton, N. Y., was born in 1864 and died at Sag Harbor, Long Island, on May 17, 1943, of coronary thrombosis; aged, 78 years.

Dr. Overton graduated from the Long Island College Hospital of Brooklyn in 1887. In 1936 he celebrated his fiftieth year in the practice of medi-

cine. He temporarily retired and spent a year in New Mexico, then returned again to Binghamton and resumed his work. Dr. Overton also was a Pharmacist and at one time owner of the Moore-Overton Hospital. For many years he was on the staff of the Binghamton City Hospital, and he served as a member of the New York State Grievance Committee, Medical Practice Act. He was a member of the Binghamton Academy of Medicine, the New York State Medical Society and a Fellow of the American Medical Association. He was a charter member of the American Congress on Internal Medicine from 1916, and by virtue of that membership became an Associate of the American College of Physicians, which membership was maintained in good standing the balance of his life.

DR. STIRLEY CASPER DAVIS

Dr. Stirley Casper Davis was born in Owenton, Ky., October 25, 1882, graduated from the Hospital Medical College, now University of Louisville School of Medicine, Louisville, Ky., in 1906. He pursued postgraduate work in various institutions in New York, New Orleans, Philadelphia and San Francisco. He entered on a medical career that was to last thirty-seven years and make him one of the best known physicians in Arizona. The first World War interrupted his medical career briefly, for he went overseas with the Thirty-fourth Division as a Captain in the Medical Corps.

In 1920, Dr. Davis arrived at Tucson where he helped found the Thomas-Davis Clinic and he became the Chief of the Medical Staff there. For many years he was Medical Director of the Southern Pacific Sanatorium. In 1927, he became President of the Chamber of Commerce and was instrumental in securing the location of the U. S. Veterans' Hospital at Tucson.

For the past thirteen years he had been a member of the Board of Tucson School District No. 1 and served virtually half of that time as its President. During his term of office, the public school system was greatly expanded and he was responsible for many improvements in working conditions and teaching personnel.

Dr. Davis had served as President of the Pima County Medical Association and as a Director of the Tucson Sunshine Climate Club. He was also a member of the Arizona State Medical Society, a Charter Member of the American College of Chest Physicians, a Fellow of the American Medical Association and, since 1930, a Fellow of the American College of Physicians.

Dr. Davis died at Tucson, March 14, 1943, of heart disease, at the age of sixty. He is survived by his wife, Mrs. Mabel Davis, and a daughter, Mrs. Harold T. Landon.

CHARLES S. KIBLER, M.D., F.A.C.P.,
Tucson, Ariz.

DR. HAROLD W. DANA

Dr. Harold W. Dana, M.D., F.A.C.P., Brookline, Mass., died of pneumonia at his home in Brookline on May 8, 1943. He was in his sixty-sixth year.

Dr. Dana was graduated from the Harvard Medical School in 1905, served two years as house officer at the Boston City Hospital and spent a year and a half in postgraduate medical study, chiefly in Berlin and Vienna. He returned to practice internal medicine in Boston and served on the Medical Staff of the Boston City Hospital, later becoming Physician-in-Chief of the First Medical Service. He was also Associate Professor of Medicine at Tufts College Medical School.

He was certified as a specialist by the American Board of Internal Medicine. He was also a Fellow of the American College of Physicians and a member of the Massachusetts Medical Association.

Besides his medical career, Dr. Dana was a man of varied interests, being an amateur watercolor painter of note. He was a prominent member of the New England Historical Genealogical Society and had also served as President of the Massachusetts Society of Sons of the American Revolution and of the Massachusetts Society of the War of 1812.

He is survived by his widow, the former Gertrude Quinn of Dover, New Hampshire; two daughters, Mrs. Patrick Brady of Brookline, and Mrs. Henry S. Bromley, Jr., of Ardmore, Pa., and five grandchildren.

WILLIAM B. BREED, M.D., F.A.C.P.,
Governor for Massachusetts